

ANNALS

OF

INTERNAL MEDICINE



PUBLISHED MONTHLY BY

THE AMERICAN COLLEGE OF PHYSICIANS

VOLUME 55 • NUMBER 1

JULY 1961

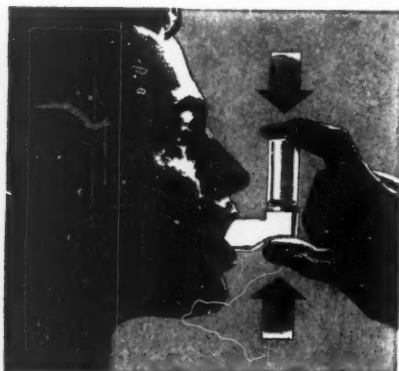
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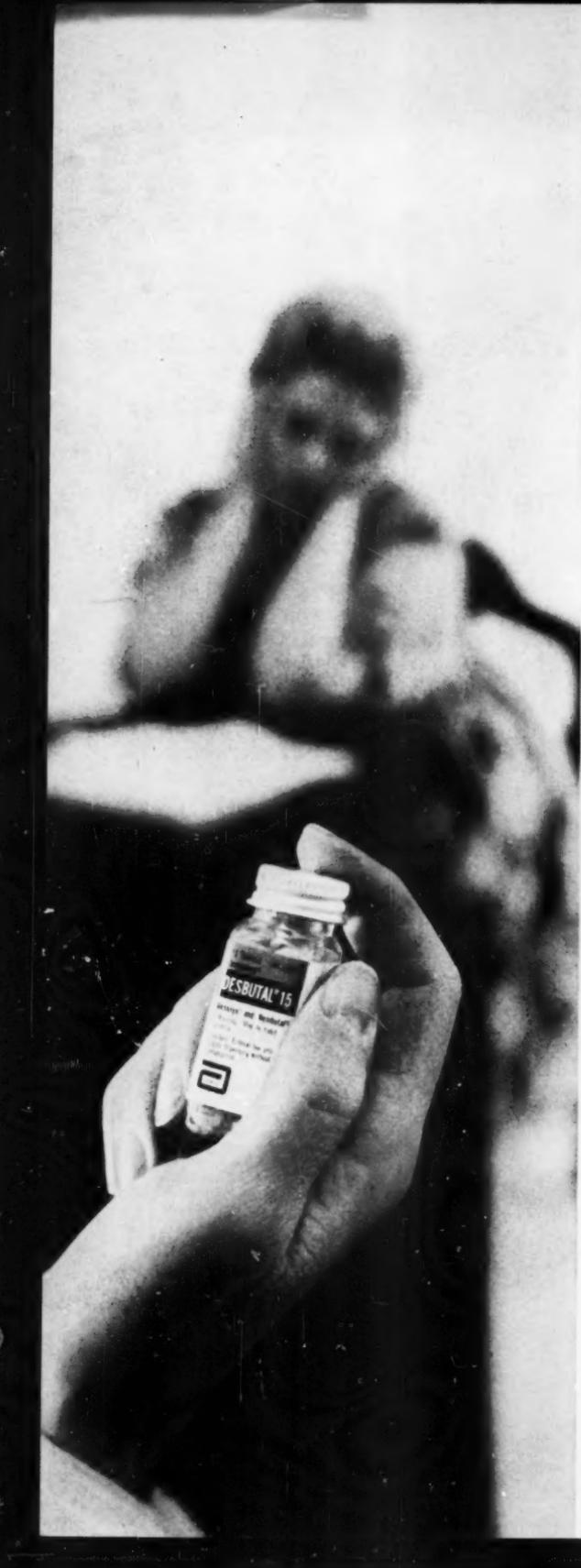
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1. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap. 83:367, 1946. 2. Melville, K.I., and Lu, F.C.: Canad. M.A.J. 65:11, 1951. 3. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy 3:322, 1956. 4. Eisfelder, H.W. et al.: J. Am. Geriatrics Soc. 8:62, 1960.

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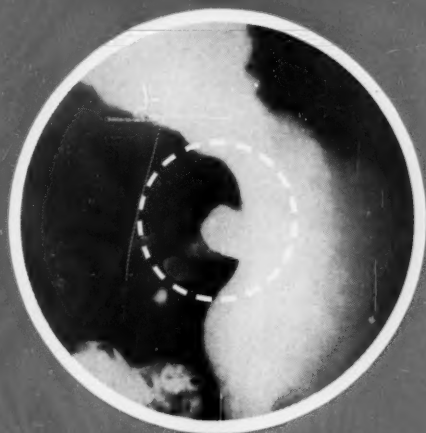
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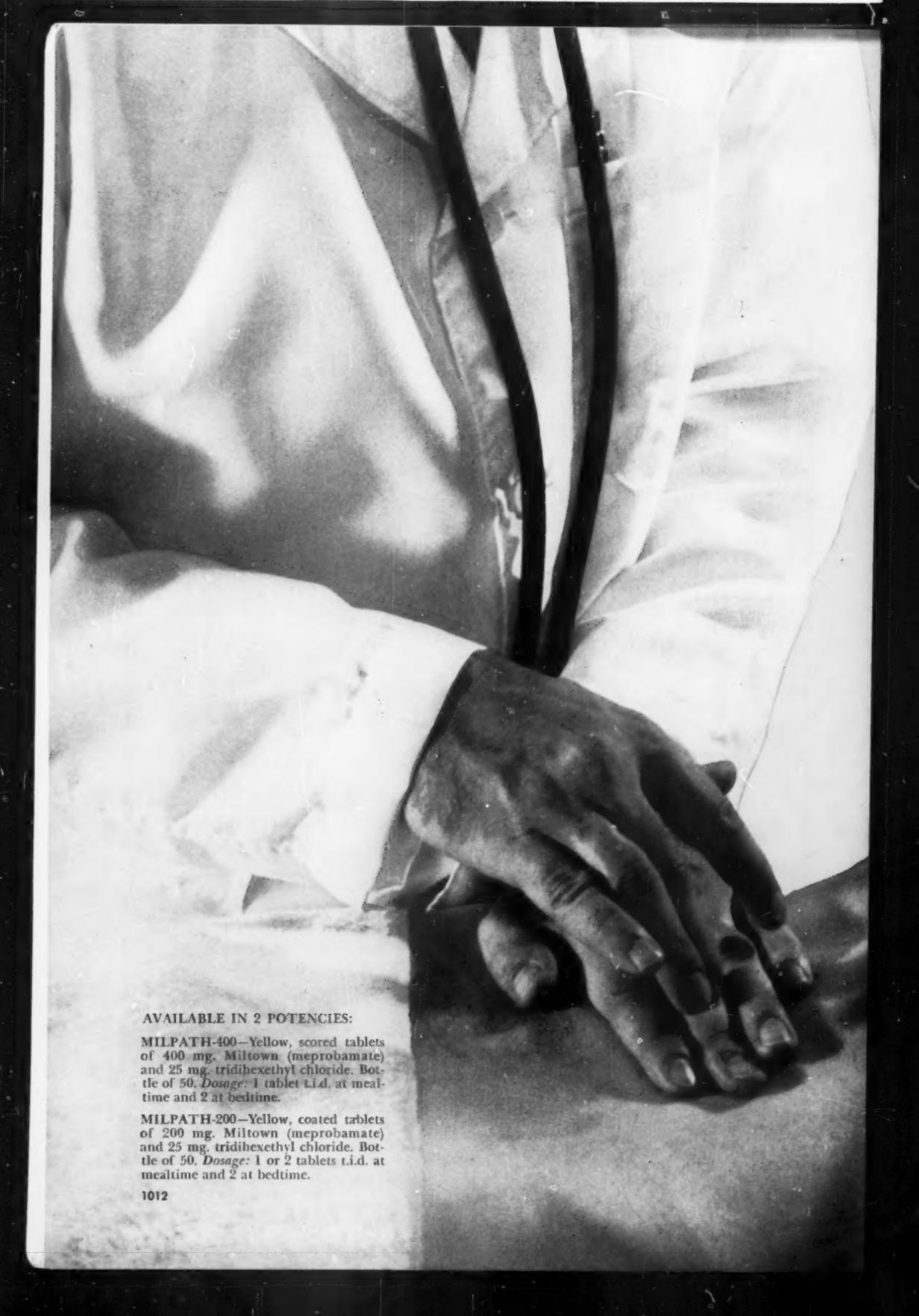
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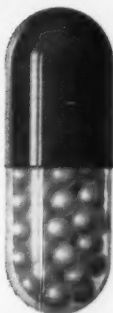
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1. Meyers, G. B.: Ind. Med. & Surg. 26:3, 1957. 2. Murray, R. J.: N. Y. St. J. Med. 53:1867, 1953.

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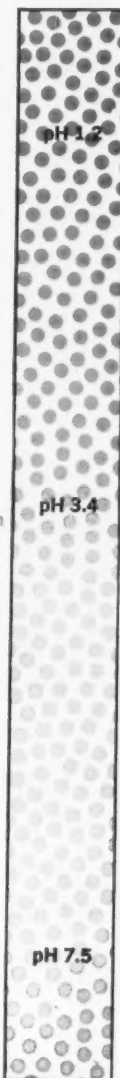


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1. Dugger, J. A.: J. Michigan M. Soc. 59:1812 (Dec.) 1960.

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Why arthritic patients feel much better on Dianabol

1. In arthritis, Dianabol improves general physical condition

Arthritis, like other chronic illnesses, plunges the body into a catabolic state. Protein stores are depleted; appetite wanes; weight drops; strength and vigor decline. By aiding the deposition, synthesis and utilization of protein, and by conserving calcium, Dianabol promotes lean weight gain, increases strength and vitality, and strengthens bone structure in patients with a wide range of chronic diseases. Recent studies show that adjunctive use of Dianabol may be particularly valuable in patients with arthritis to improve over-all clinical status. Kuzell and Naugler,¹ for example, report that arthritic patients on Dianabol "generally have experienced an increase in appetite, weight, strength and endurance." Kuzell and Naugler note further: "Unlike some other testosterone derivatives, the use of this compound [Dianabol] is not followed by virilizing phenomena. Fluid retention has been no problem."

2. In arthritis, Dianabol helps restore a sense of well-being

Plagued by pain and reduced mobility, arthritics often lose hope and become depressed. The marked improvement in general health usually associated with therapy with Dianabol may have a favorable effect in these patients, as it has in so many chronically ill individuals. As physical status improves, hope is revived and a sense of well-being restored. Commenting on the use of Dianabol in a group of debilitated, cachectic patients, Gingrich² states: "The majority of patients experienced increase in appetite and a feeling of well-being."

3. In arthritis, Dianabol augments the beneficial effects of salicylates, corticosteroids, etc.

Several investigators^{1,3,4} have observed improved therapeutic response after the addition of Dianabol to antiarthritis regimens. Kuzell and Naugler¹ state: "In generalized osteoarthritis, symptoms have been less bothersome, and in ankylosing spondylitis gain in weight and strength has followed the use of Dianabol." Clark,³ reporting on 12 hospitalized patients with rheumatoid arthritis being given moderate to large doses of corticosteroids with evidence of steroid intoxication, noted that the addition of Dianabol promptly decreased joint symptoms but increased steroid intoxication. However, with Dianabol it was possible to reduce corticosteroid dosage considerably, while maintaining and even furthering clinical improvement. In 15 ambulatory patients on small maintenance doses of corticosteroids, the addition of Dianabol resulted in further clinical improvement which was continued even when corticosteroid dosage was reduced in some cases.^{3,4}

4. In arthritis, Dianabol counteracts the catabolic effects of corticosteroids

Prolonged use of corticosteroids may result in excessive breakdown of protein in all tissues, including bone,⁵ as well as undue phosphorus and calcium loss.⁶ If protein destruction is allowed to go unchecked, it may lead to osteoporosis—a condition that has occurred with increasing frequency in patients receiving corticosteroids for extended periods.⁷ Tillis⁸ asserts that it is "imperative" to restore the protein bone matrix in such patients

through the use of an anabolic agent. He studied the specific anabolic benefits of Dianabol in 50 patients with osteoporosis (34 postmenopausal and 16 corticosteroid-induced), most of whom also had rheumatoid arthritis. Dianabol relieved bone pain, increased strength and vigor, and induced a sense of well-being in 41 (82 per cent) of these patients. Edema, observed in 8 patients, was cleared in 4 by reduction of dosage; the remaining 4 responded promptly to hydrochlorothiazide. Gastric distress was noted in 2 patients, slight hoarseness in 1 woman, and facial acne in 1 woman. Other investigators^{8,9} have shown that addition of Dianabol to the regimens of patients receiving corticosteroids improved nitrogen and potassium metabolism and reduced phosphorus and calcium losses. Reporting on 10 patients taking corticosteroids, most of whom had corticosteroid-induced osteoporosis and/or myopathy, Abbott⁹ states: "In the patients who showed a markedly negative nitrogen balance the administration of 10 mg. of Dianabol per day greatly reduced the protein deficit. In others who were eating well and taking smaller amounts of corticosteroids a positive nitrogen balance resulted which increased with Dianabol." Abbott notes that creatinuria, which occurred on corticosteroids alone, was increased by Dianabol, as it is by methyltestosterone and the newer oral methyl- or ethyl-testosterone derivatives. However, he observes that the "significance of this creatinuria is not known and no ill effects have been ascribed to this change." While the finding of elevated serum aldolase levels raised the theoretical possibility of potentially deleterious effects, Vignos *et al*⁸ and Abbott⁹ noted no androgenic or myopathic effects and no liver disorders in patients who took Dianabol and corticosteroids for up to 8 months. Kuzell

and Naugler¹ state it is their impression that Dianabol has checked weight loss following prolonged administration of triamcinolone in patients with rheumatoid arthritis. They add that, with Dianabol, protein patterns have migrated toward normal profiles, purpura consequent to corticosteroid administration has been lessened, and the erythrocyte sedimentation rate has been diminished.

advantages of Dianabol over other anabolic agents as an adjunct in the treatment of arthritis

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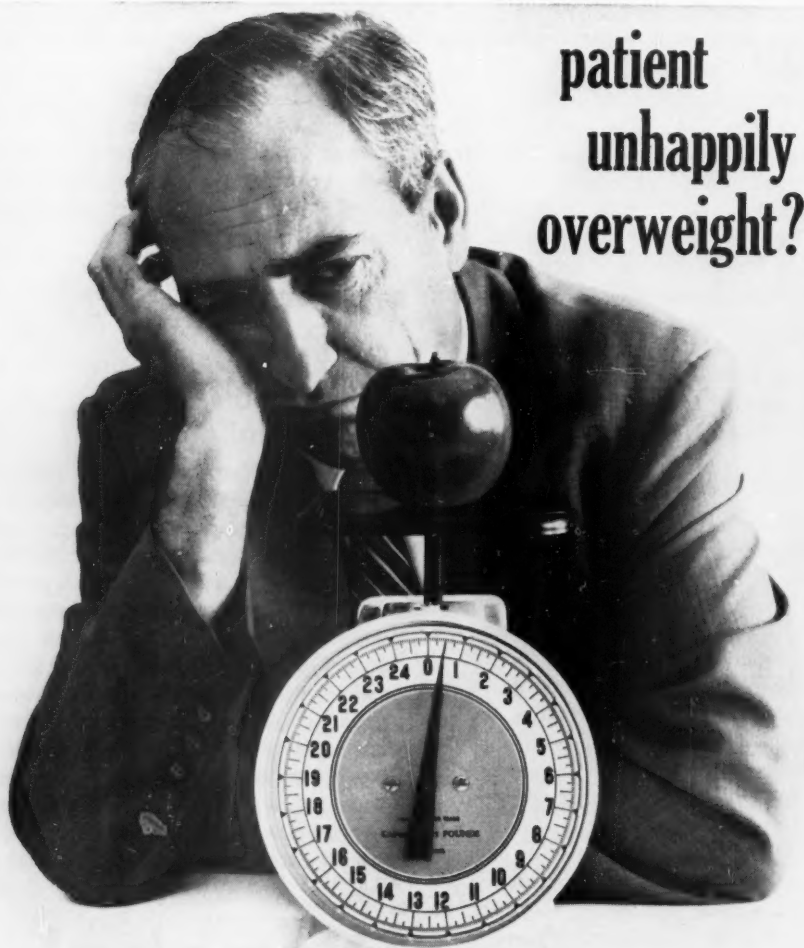
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REFERENCES: 1. Kuzell, W. C., and Naugler, W. E.: Paper presented at the Annual Meeting of the American Rheumatism Association, Hollywood-By-The-Sea, Florida, June 9-11, 1960. 2. Gingrich, G. W.: Clinical report to CIBA. 3. Clark, G. M.: Paper presented at the Seventh Interim Session of the American Rheumatism Association, Dallas, Texas, Dec. 10, 1960. 4. Clark, G. M., Kaplan, S., Goobar, J., and Mills, D.: Arthritis and Rheumatism 4:106 (Feb.) 1961. 5. Tillis, H. H.: Clin. Med. 8:274 (Feb.) 1961. 6. Lockie, L. M.: J.A.M.A. 170:1063 (June 27) 1959. 7. Boland, E. W.: J.A.M.A. 150:1281 (Nov. 29) 1952. 8. Vignos, P. J., Jr., Abbott, W. E., Post, R. S., and Levy, S.: J. Lab. & Clin. Med. 56:954 (Dec.) 1960. 9. Abbott, W. E.: Research report to CIBA. 10. Misraile, F.: Minerva med. 51:996 (March 21) 1960.



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¹ Douglas, H. S.: West. J. Surg. 59:238 (May) 1951.



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¹Hobbs, L. E. VIRGINIA M. MONTH. 85:692, (December) 1959.



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references

- (1) Pareira, M. D., et al.: J.A.M.A. 156:810-816 (Oct. 30) 1954.
(2) Winkelstein, A.: Am. J. Gastroenterol. 27:45-52 (Jan.) 1957.



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**ANNOUNCING... A POTENT
ANTIDEPRESSANT
WITH EFFECTIVE
ANTI-ANXIETY
PROPERTIES...**

NEW

ELAVIL

AMITRIPTYLINE HYDROCHLORIDE



**new...a potent
antidepressant
with effective
anti-anxiety
properties**

EL

AMITRIPTYLINE HYDROCHLORIDE

RELATIVE UTILITY IN MANAGEMENT OF DEPRESSED PATIENTS				
Class of compounds	TARGET SYMPTOMS OF DEPRESSION:			
	Anxiety	Insomnia	Depression	Over-all relief of symptoms
TRANQUILIZERS	"Failure of the tranquilizers to produce satisfactory results is due in many cases to their being prescribed for depression, especially depression masked by the more prominent symptoms of anxiety. The underlying depression may be deepened."			+ —
ANTIDEPRESSANTS			"CNS stimulants and anti-depressants, if given to anxious patients, will increase the anxiety..."	+
ELAVIL	"... this drug [ELAVIL] acted both as a tranquilizer and as an anti-depressant..." ² Many physicians customarily treat anxious or depressed patients with a combination of an antidepressant and a tranquilizer. This is seldom necessary when prescribing ELAVIL because it has both antidepressant and anti-anxiety properties.			++

AVIL

*effective in patients with depression...
particularly useful in those with predominant symptoms
of anxiety and tension...provides prompt relief of anxiety
and insomnia associated with depression*

SPAN OF ACTIVITY OF PSYCHOACTIVE DRUGS	
TRANQUILIZERS	ANTIDEPRESSANTS
ELAVIL	

INDICATIONS: manic-depressive reaction — depressed phase; involuntal melancholia; reactive depression; schizo-affective depressions; neurotic depressive reaction; and these target symptoms: anxiety; depressed mood; insomnia; psychomotor retardation; functional somatic complaints; loss of interest; feelings of guilt; anorexia. May be used whether the emotional difficulty is a manifestation of neurosis or psychosis, and in ambulatory or hospitalized patients.^{3, 4, 5}

USUAL ADULT ORAL DOSAGE: Initial, 25 mg. three times a day, until a satisfactory response is noted. Many patients improve rapidly, although some depressed patients may require four to six weeks of therapy before obtaining maximum benefit. In severely depressed patients, as much as 150 mg. per day may be given. Maintenance, 25 mg. two to four times a day. Some patients may be maintained on 10 mg. four times a day. The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstituted.

ELAVIL is not a monoamine oxidase (MAO) inhibitor. No evidence of drug-induced jaundice or agranulocytosis has been noted. Side effects (drowsiness, dizziness, nausea, excitement, hypotension, fine tremor, jitteriness, headache, heartburn, anorexia, increased perspiration, and skin rash), when they occur, are usually mild. However, as with all new therapeutic agents, careful observation of patients is recommended. As with other drugs possessing significant anticholinergic activity, ELAVIL is contraindicated in patients with glaucoma.

SUPPLY: Tablets, 10 mg. and 25 mg., in bottles of 100. Injection (intramuscular), 10 mg. per cc., 10-cc. vials.

REFERENCES: 1. Perloff, M. M., and Levick, L. J.: Clinical Med. 7:2237, Nov. 1960. 2. Freed, H.: Am. J. Psychiat. 117:455, Nov. 1960. 3. Dorfman, W.: Psychosomatics 1:153, May-June 1960. 4. Ayd, F. J., Jr.: Psychosomatics 1:320, Nov.-Dec. 1960. 5. Barse, J. A., and Saunders, J. C.: Am. J. Psychiat. 117:739, Feb. 1961.

Before prescribing or administering ELAVIL, the physician should consult the detailed information on use accompanying the package or available on request.



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your "doctor's
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Vitamin B₁₂ 4 mcgm.
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Average dose: 1 to 2 capsules daily.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.



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DUST:

a threat in
chronic bronchitis,
chronic asthma
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but it needn't trigger a respiratory crisis

You can't isolate the patient with chronic respiratory disease from all potential irritants. That is why Choledyl prophylaxis is essential. Taken regularly — daily — Choledyl helps prevent severe respiratory flare-ups by affording continuous relief from debilitating bronchospasm. Throughout long-term use, Choledyl is uniformly effective. And even in older patients, gastric upset and other unwanted effects are rare.

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GP 13

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The action of Dulcolax is based on simple reflex production of large bowel peristalsis on contact with the colonic mucosa. As a result, stools are usually soft and well formed and purgation is avoided.

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Dulcolax is as well adapted to preparation for radiographic and operative procedures as it is to the treatment of constipation.

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Dulcolax[®], brand of bisacodyl: Tablets of 5 mg. and suppositories of 10 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

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DU 568-60 

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is gentle, safe, sure, dietary

It's available in two forms, liquid and powder, but most adults prefer the mild tasting powder. It dissolves instantly in milk, water or juices. It promotes aciduric flora in the lower bowel which helps restore normal function. Long term treatment produces no side effects. Diabetic patients should allow for 60 calories for each tablespoonful.

Hootnick⁽¹⁾ reports, "Stools became soft in all patients and, within one week, bowel evacuations were accomplished with ease. Most patients liked the taste of the product, and the majority of them reported a feeling of well-being."

Dose: 2 tablespoonfuls twice a day. Available, liquid and powder, 8 ounce and 16 ounce bottles, at pharmacies.

Send for clinical samples

(1) Hootnick, H. L.: Jnl. Amer. Ger. Soc., 4:1021-1030, 1956.

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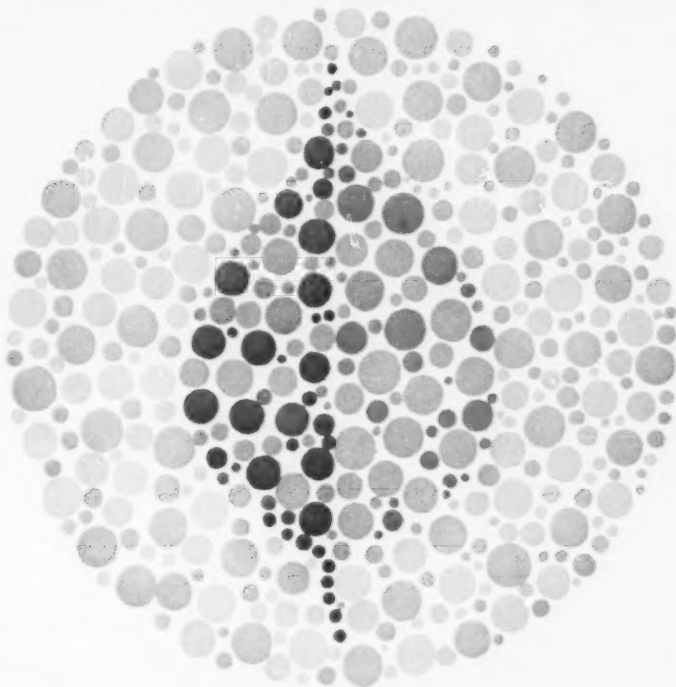
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for maximal digitalis activity with minimal toxicity

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"...patients who became toxic very readily with other agents could later be satisfactorily digitalized with gitalin (GITALIGIN)."²

Wider margin of safety—frequently effective in patients refractory to other digitalis glycosides • broader clinical utility—therapeutic dose only $\frac{1}{3}$ the toxic dose • faster rate of elimination than digitoxin or digitalis leaf. □ Supplied: 0.5 mg. scored tablets—bottles of 30 and 100.

1. Dimitroff, S. P. et al.: Ann. Int. Med. 39:1189, 1953. 2. Pastor, B. H.: GP 22:85, 1960.

†amorphous gitalin, White



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RECOVERY RATE: OVER 90%

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*"... at present, this is the oral
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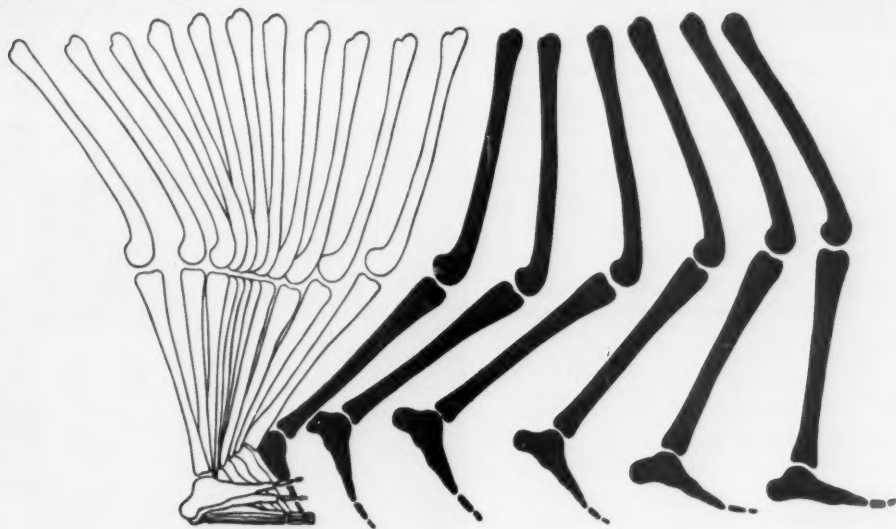
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*"... Safe and effective anticoagulant
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HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.



Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these.¹ "Post-injection flare-up was practically non-existent."¹

Indications and dosages

Intra-articular, intrabursal and intra-tendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.

Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.

Each cc. contains:

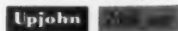
Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, *New York J. Med.* 61:552 (Feb. 15) 1961.

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**relief
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THERAPEUTIC INDEX

"Thiosulfil" Forte 0.5 Gm. Tablet

BRAND OF SULFAMETHIZOLE

"THIOSULFIL" has been found effective against the following urinary pathogens: *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus fecalis*, *Escherichia intermedium*, and *Aerobacter aerogenes*. In individual cases, sensitivity of the organisms may vary. Sensitivity tests, preferably by the tube dilution method, should be done first, for guidance as to alternate therapy in case "THIOSULFIL" FORTE does not control the infection.

INDICATIONS: Treatment of cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis due to bacterial infection amenable to sulfonamide therapy; prior to and following genitourinary surgery and instrumentation; prophylactically, in patients with indwelling catheters, ureterostomies, urinary stasis, and cord bladders.

SUGGESTED RANGE OF DOSAGE: Adults: 1 or 2 tablets (0.5 Gm.-1.0 Gm.) three or four times daily.

WARNING: Due to the high solubility in body fluids of "THIOSULFIL" and its acetyl form, the hazards of renal tubule obstruction are minimized. The usual precautions exercised with sulfa drugs generally should, however, be observed. In those rare instances where exanthemata, urticaria, nausea, emesis, fever or hematuria, are encountered, administration should be discontinued.

CONTRAINDICATION: A history of sulfonamide sensitivity.

SUPPLIED: NO. 786 — "THIOSULFIL" FORTE — Each tablet contains sulfamethizole 0.5 Gm. (scored), in bottles of 100 and 1,000.

ALSO AVAILABLE — NO. 785: "THIOSULFIL" — Each tablet contains sulfamethizole 0.25 Gm. (scored), in bottles of 100 and 1,000. No. 914 — "THIOSULFIL" Suspension — Each 5 cc. (teaspoonful) contains sulfamethizole 0.25 Gm., in bottles of 4 and 16 fluidounces.

SUGGESTED DOSAGES: Infants and children: The dosage is scheduled on an average basis of $\frac{1}{2}$ to $\frac{3}{4}$ gr. (30 to 45 mg.) per pound of body weight per day in divided doses. Maximum dosage up to 50 lbs., $\frac{1}{2}$ teaspoonful q.i.d. Maximum dosage from 50 to 75 lbs., 1 teaspoonful q.i.d.

WHEN ANALGESIA IS DESIRED

"THIOSULFIL"-A FORTE NO. 783:

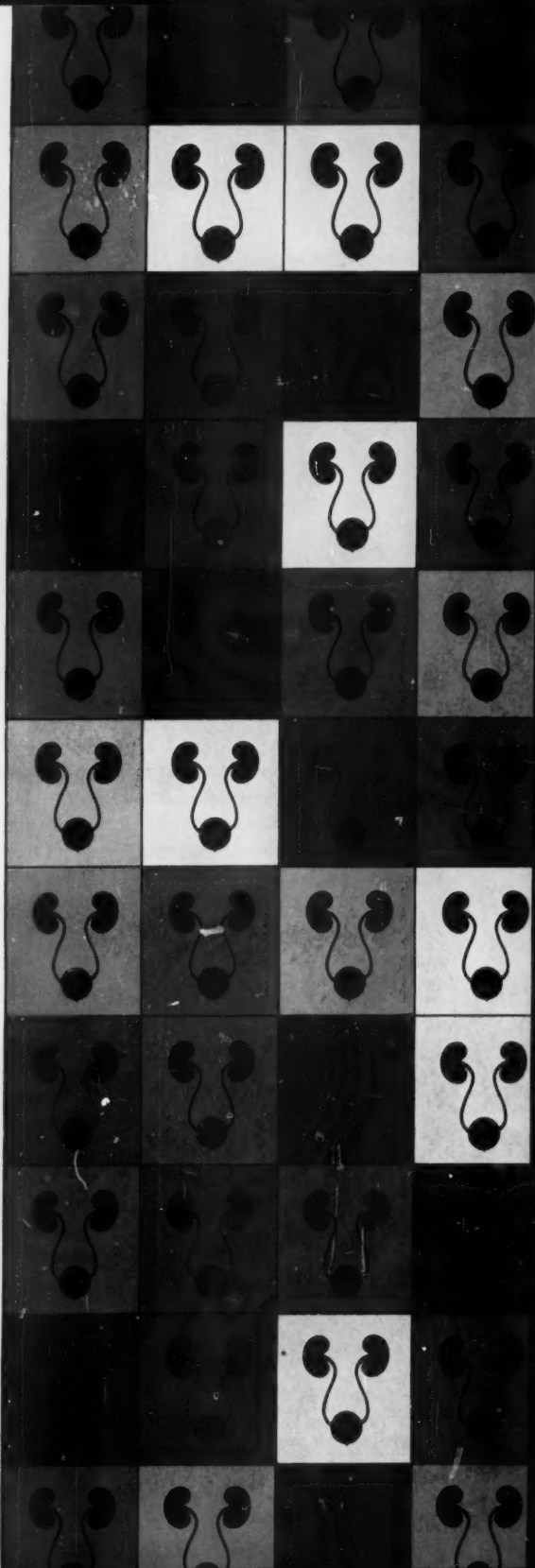
Each tablet contains sulfamethizole 0.5 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

CONTRAINDICATIONS: (1) a history of sulfonamide sensitivity and (2) due to the phenylazo-diamino-pyridine HCl component, renal and hepatic failure, glomerulonephritis, and pyelonephritis of pregnancy with gastrointestinal disturbances.

USUAL DOSAGE: Adults: 2 tablets, four times daily. Children (9 to 12 years): 1 tablet, four times daily.

ALSO AVAILABLE: NO. 784 "THIOSULFIL"-A — Each tablet contains sulfamethizole 0.25 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000. **USUAL DOSAGE:** Adults: 2 tablets, four times daily. Children (9 to 12 years): 1 tablet, four times daily.

For references, see opposite page.



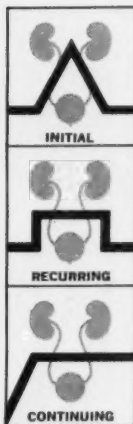
SAFELY MANAGES ALL EPISODES OF URINARY TRACT INFECTION

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THE ONE SULFONAMIDE THAT OFFERS

- Maximum urinary concentration of active, free sulfa at site of infection
- Rapid clearance (noncumulative)
- Rare incidence of side effects
- High degree of clinical effectiveness

"Thiosulfil" dosage schedules reported in the literature.



INITIAL EPISODE (Acute Infection) 3 Gm./day¹

Based on 7 years' clinical experience in treating 3,057 cases of upper and lower urinary tract infection, Bourque¹ found 3 Gm./day for 2 weeks (the average dosage employed in 97 per cent of patients) effective in most cases.

RECURRING EPISODE (Flare-up) 3 Gm./day¹

Same dosage as above. When longer therapy is required as in cases where there is stasis due to obstruction, administration may be continued at a lower dosage range.

CONTINUING EPISODE (Stasis/Obstruction) 2 Gm./day^{2,3} 0.5 Gm./day⁴

Where infection remains latent due to causes which cannot be eliminated as in paraplegia, patients have been maintained symptom-free on dosage regimens ranging from 2 Gm. to 0.5 Gm./day. After initial control of acute symptoms, therapy may be continued indefinitely on a low dosage basis to guard against recurrence and prevent ascending infection. Many cases can be controlled with as little as 0.5 Gm./day.

SUPPLIED: No. 786 — "Thiosulfil" Forte — Each tablet contains sulfamethizole 0.5 Gm. (scored), in bottles of 100 and 1,000.

ALSO AVAILABLE — In urinary tract infection—to alleviate pain and control the infection: No. 783 — "THIOSULFIL"®-A FORTE combines the sulfonamide specific for urinary tract infection with a potent analgesic for prompt, soothing relief of local discomfort. Each tablet contains sulfamethizole 0.5 Gm. and phenylazo-diamino-pyridine HCl 50 mg., in bottles of 100 and 1,000 tablets.

References: 1. Bourque, J.-P., and Gauthier, G.-E.: L'Union Medicale 88:640 (May) 1980. 2. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 56:86 (Mar.) 1959. 3. Bourque, J.-P., and Joyal, J.: Canad. M.A.J. 88:337 (Apr.) 1963. 4. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.



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THE URINE-SPECIFIC ANALGESIC/ANTIBACTERIAL

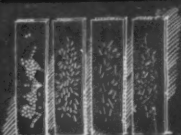
in common lower urinary infections



controls urinary infection without producing resistant mutants



relieves urinary pain in 30 minutes



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sensitization and other systemic reactions do not develop



well tolerated



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Composition: Each Azo-Mandelamine tablet contains 50 mg. phenylazodiamine-pyridine HCl (Pyridium®) and 500 mg. methenamine mandelate (Mandelamin®). **Average Adult Dosage:** Two Azo-Mandelamine tablets four times a day. **Precautions:** Azo-Mandelamine is contraindicated in patients with renal insufficiency and/or severe hepatitis. An occasional patient may experience gastrointestinal disturbance. Full dosage information, available on request, should be consulted before initiating therapy.

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New
diuretic-tranquilizer
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- Controls edema
- Relieves anxiety

Miluretic combines hydrochlorothiazide and Miltown in a single tablet, making treatment simpler for you and more economical for your patient.

Miluretic's hydrochlorothiazide component provides smooth, continuous diuresis to control edema, while its Miltown component relieves the anxiety associated with congestive failure — with an outstanding degree of safety.

Economy A prescription for Miluretic is more than 20% cheaper than its two ingredients prescribed separately.

Composition: 25 mg. hydrochlorothiazide + 200 mg. Miltown (meprobamate).

Dosage: For congestive failure, 2 tablets four times a day. For hypertension, 1 tablet four times a day.

Supplied: Bottles of 50 white, scored tablets.

new **Miluretic**^{*}
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In the "secondary" anemias due to chronic disease or infection, iron alone is often ineffective since its utilization is impeded by depressed bone marrow activity. However, RONCOVITE[®]-MF (cobalt-iron) has proved notably effective in these iron-refractory anemias^{1,2} because of the unique marrow-activating effect of cobalt-created erythropoietin, the hormone which controls the rate of erythropoiesis. Thus, RONCOVITE-MF improves iron utilization and produces rapid increases in hemoglobin and red blood cell formation.^{3,4}

Each tablet contains: Cobalt chloride, 15 mg. (cobalt as Co, 3.7 mg.) and ferrous sulfate exsiccated, 100 mg.

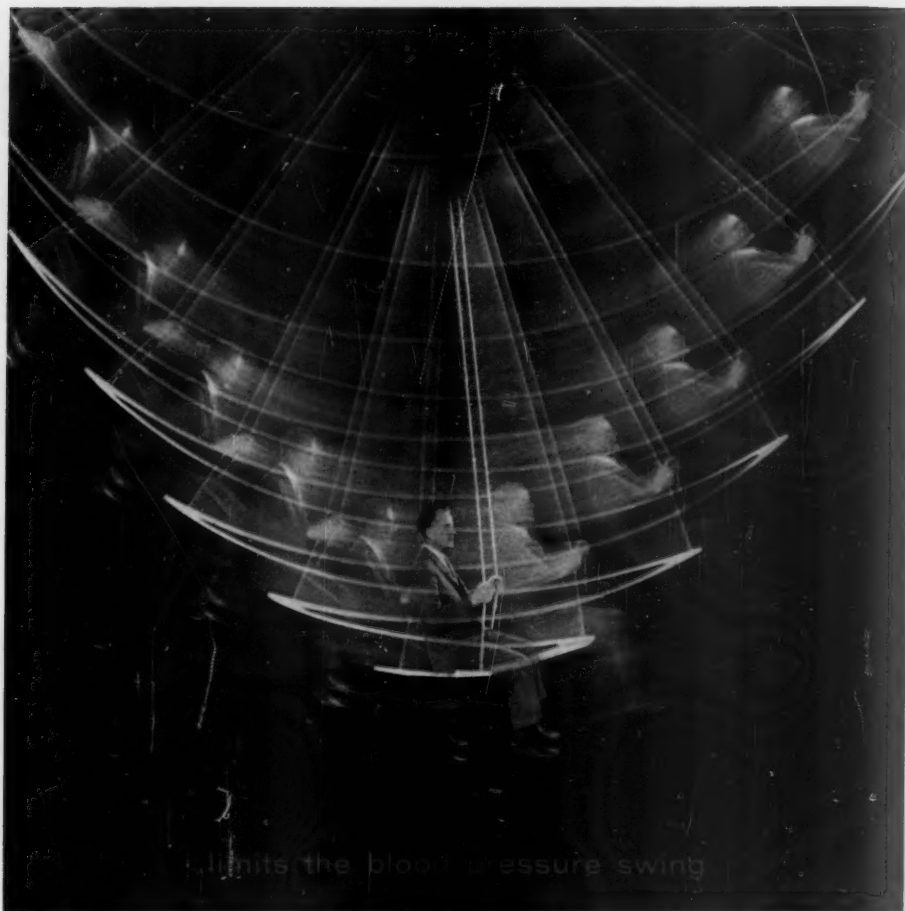
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RONCOVITE[®]-mf



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limits the blood pressure swing

Rautrax-N lowers high blood pressure gently, gradually . . . protects against sharp fluctuations in the normal pressure swing.

Rautrax-N offers all the advantages of Raudixin, Naturetin and potassium chloride in a single dosage form *plus*: *increased efficacy* — Combined action of Raudixin and Naturetin results in a potentiated antihypertensive effect greater than that produced by either drug alone. *increased safety* — Potentiated action permits lower dose of other antihypertensive agents, thus reducing severity of side effects. Protection against possible potassium depletion. *flexibility* — Interchangeable

with either Raudixin or Naturetin \bar{c} K. *economy* — Maintenance dosage of only 1 or 2 tablets daily for most patients. *convenience* — Once-a-day maintenance dosage. Two potencies available.

Supply: Rautrax-N — capsule-shaped tablets providing 50 mg. Raudixin, 4 mg. Naturetin and 400 mg. potassium chloride. *Rautrax-N Modified* — capsule-shaped tablets providing 50 mg. Raudixin, 2 mg. Naturetin and 400 mg. potassium chloride.



Rautrax-N*

Squibb Standardized Whole Root Rauwolfia Serpentina (Raudixin) and Bendroflumethiaside (*Naturetin) with Potassium Chloride

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*the first complete
physiologic regulator of
female cyclic function*

ENOVID®

(BRAND OF NORTHYNOXOL WITH ETHINYLESTRADIOL 3-METHYL ETHER)

The basic action

ENOVID closely mimics the balanced progestational-estrogenic action of the functioning corpus luteum. This action is readily understood by a simple comparison. In effect, ENOVID induces a physiologic state which simulates early pregnancy—except that there is no placenta or fetus. Thus, as in pregnancy, the production or release of pituitary gonadotropin is inhibited and ovulation suspended; a pseudodecidual endometrium ("pseudo" because neither placenta nor fetus is present) is induced and maintained. Further, during ENOVID therapy, certain symptoms typical of normal pregnancy may be noted in some patients, such as nausea—which is usually mild and disappears spontaneously within a few days—breast engorgement, some degree of fluid retention, and often a marked sense of well-being. There is no androgenicity. ENOVID is as safe as the normal state of pregnancy.

The basic applications

1. Correction of menstrual dysfunction. Cyclic therapy with ENOVID controls dysfunctional uterine bleeding (menorrhagia, metrorrhagia) and often establishes a normal menstrual cycle in amenorrhea.

2. Ovulation suppression (to suspend fertility). For this purpose ENOVID is administered cyclically, beginning on day 5 through day 24 (20 daily doses). The ovary remains

in a state of physiologic rest and there is no impairment of subsequent fertility. Continuous administration for more than two years is not recommended.

3. Postponement of the menses for reasons of health (impending hospitalization for surgery, during treatment of Bartholin's gland cysts, acute urethritis, rectal abscess, trichomonal or monilial vaginitis), travel, forthcoming marriage, or pressing business or professional engagements. For this purpose ENOVID may be started at any time in the cycle up to one week before expected menstruation. Upon discontinuation, normal cyclic bleeding occurs in three to five days.

4. Threatened abortion. Continuous ENOVID treatment provides balanced hormonal support for the endometrium in threatened or habitual abortion.

5. Endocrine infertility. ENOVID has been used successfully in cyclic therapy of endocrine infertility, promoting subsequent pregnancy through a probable "rebound" phenomenon.

6. Endometriosis. Continuous therapy with ENOVID corrects endometriosis by producing a pseudodecidual reaction with subsequent absorption of aberrant endometrial tissue.

The basic dosage

Basic dosage of ENOVID is 5 mg. daily in cyclic therapy, beginning on day 5 through day 24 (20 daily doses). Higher doses may be used with complete safety to prevent or control occasional "spotting" or breakthrough bleeding during ENOVID therapy, or for rapid effect in emergency treatment of dysfunctional bleeding and threatened abortion. ENOVID is available in tablets of 5 mg. and 10 mg. Literature and references, covering over five years of intensive clinical study, available on request.

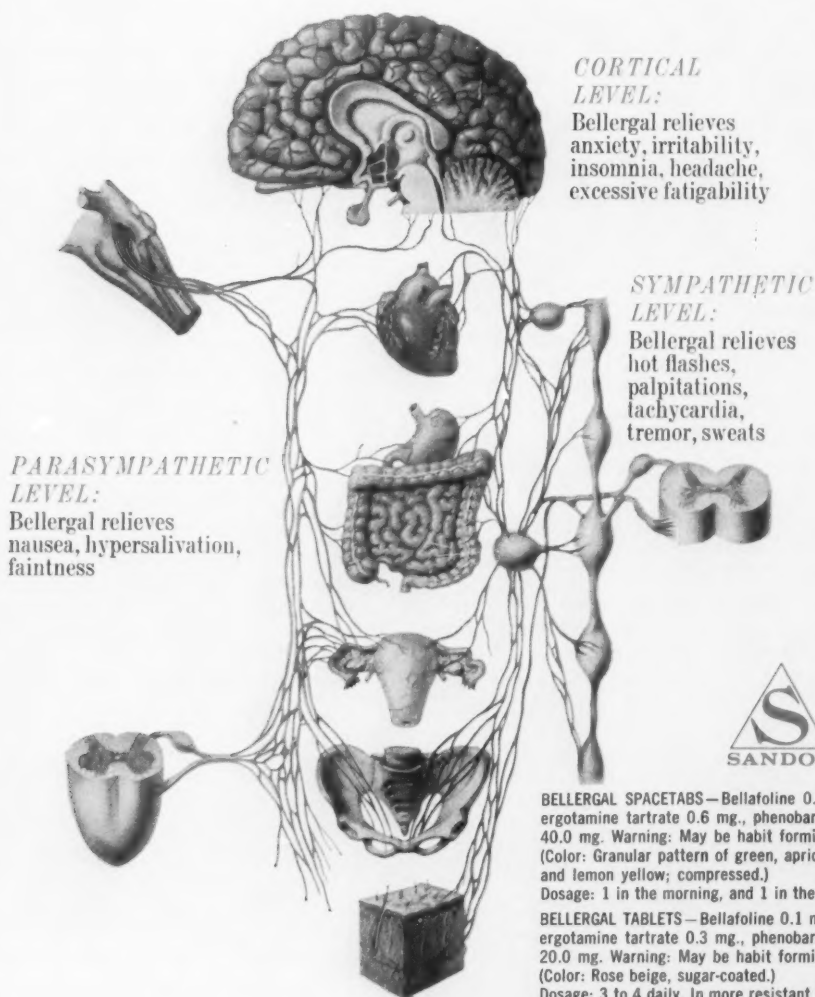
SEARLE Research in the Service of Medicine

...unfettered

From the beginning, woman has been a vassal to the temporal demands—and frequently the aberrations—of the cyclic mechanism of her reproductive system. Now, to a degree heretofore unknown, she is permitted normalization, enhancement, or suspension of cyclic function and procreative potential. This new physiologic control is symbolized in an illustration borrowed from ancient Greek mythology—Andromeda freed from her chains.

Menopausal distress: a syndrome involving all three levels of the autonomic nervous system

for functional disorders of the menopause **Bellergal**[®]
SPACETABS[®]
stabilizes the entire autonomic nervous system
(without disturbing endocrine balance)



**CORTICAL
LEVEL:**

Bellergal relieves
anxiety, irritability,
insomnia, headache,
excessive fatigability

**SYMPATHETIC
LEVEL:**

Bellergal relieves
hot flashes,
palpitations,
tachycardia,
tremor, sweats

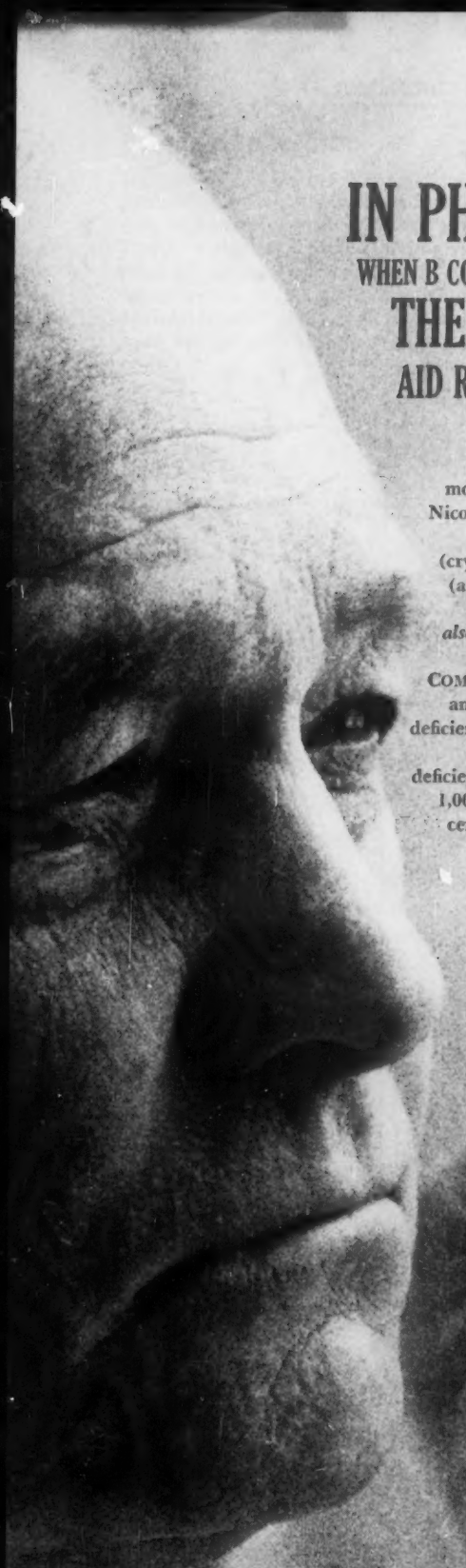
**PARASYMPATHETIC
LEVEL:**

Bellergal relieves
nausea, hypersalivation,
faintness



BELLERGAL SPACETABS—Bellafoline 0.2 mg.,
ergotamine tartrate 0.6 mg., phenobarbital
40.0 mg. Warning: May be habit forming.
(Color: Granular pattern of green, apricot
and lemon yellow; compressed.)
Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS—Bellafoline 0.1 mg.,
ergotamine tartrate 0.3 mg., phenobarbital
20.0 mg. Warning: May be habit forming.
(Color: Rose beige, sugar-coated.)
Dosage: 3 to 4 daily. In more resistant cases,
dosage begins with 6 tablets daily
and is slowly reduced.



IN PHYSIOLOGIC STRESS

WHEN B COMPLEX OR VITAMIN C DEFICIENCIES EXIST

THERA-COMBEX® KAPSEALS®

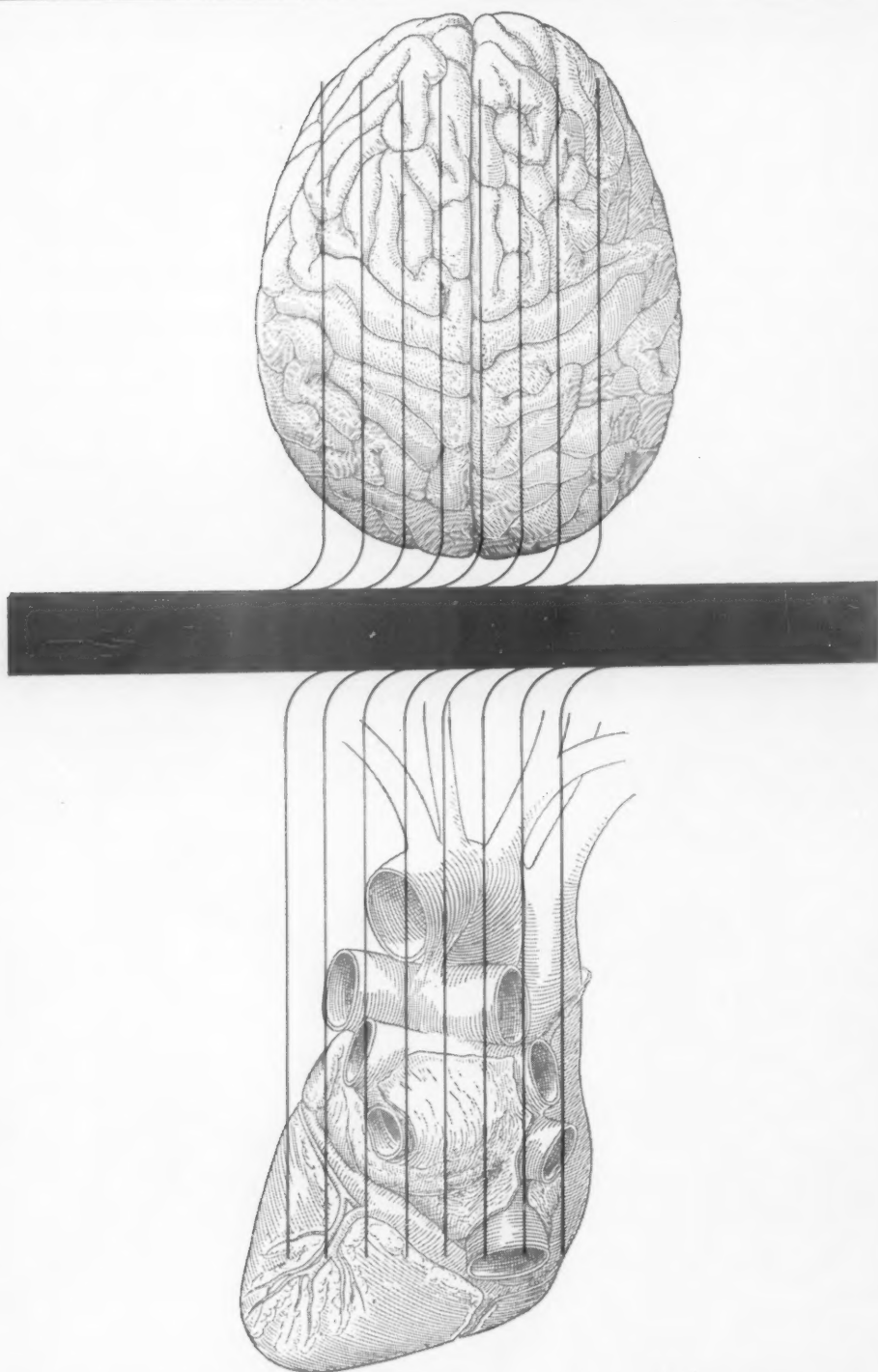
AID RECOVERY IN THE POSTOPERATIVE PERIOD AND IN CONVALESCENCE

Each Kapseal contains: Vitamin B₁ (thiamine) mononitrate—25 mg.; Vitamin B₂ (riboflavin)—15 mg.; Nicotinamide—100 mg.; Folic acid—0.1 mg.; Vitamin B₆ (pyridoxine hydrochloride)—1 mg.; Vitamin B₁₂ (crystalline)—5 mcg.; *dl*-Panthenol—20 mg.; Vitamin C (ascorbic acid)—150 mg.; Taka-Diastase® (Aspergillus oryzae enzymes)—2½ gr. Bottles of 100 and 1,000, also available: COMBEX® KAPSEALS, bottles of 100, 500, and 1,000, for prevention of B complex deficiencies. COMBEX with VITAMIN C KAPSEALS, bottles of 100, 500, and 1,000, for prevention of B complex and vitamin C deficiencies. COMBEX PARENTERAL, 10-cc. Steri-Vials®, for prevention and treatment of vitamin B complex deficiencies. TAKA-COMBEX® KAPSEALS, bottles of 100 and 1,000, for use as a digestive agent and for prevention of certain vitamin B complex and vitamin C deficiencies.

TAKA-COMBEX ELIXIR,
22961 bottles of 16 fl. oz.

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 22, Michigan



To lift depression

Marplan covers the broad range of depressive states, including seemingly mild but progressively deteriorating conditions, many "masked" depressions, suicidal ideation, as well as depressions necessitating hospitalization. It increases accessibility of the withdrawn or regressed individual, improving rapport between physician and patient.

Where prior therapy has failed, Marplan often produces dramatic results. Prompt social recovery, e.g., was achieved with Marplan in a "severe, chronic, obsessive-compulsive neurotic illness" of 20 years' duration, disabling the patient for 12 years; previous treatment had included tranquilizers and ECT.⁶

A single agent, with two distinct primary effects, for two important clinical indications

Marplan

a happy balance of potency/safety

To control pain in "difficult" cases of angina pectoris

Marplan prevents anginal pain,¹⁻³ increases exercise tolerance^{2,4,5} and reduces nitroglycerin requirements.^{2,3} It is designed for use on a continuous schedule by patients with moderately severe to intractable angina pectoris.

Marplan improves the mental climate: Not only could anginal patients placed on Marplan "... do more than formerly ..." but they also felt better, were more alert, more cheerful.^{2,4} The loss of pain as a warning signal against undue exertion may be balanced by close patient supervision, strict guidance, and by maintaining all restrictions of activity in force prior to Marplan therapy.

Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. One might expect such potency to be associated clinically with increased side effects. Actually, Marplan strikes a happy balance of potency and safety, exhibiting a marked decrease in certain of the hydrazine side reactions; there have been no reports of hepatitis attributable to Marplan. Nevertheless, all precautions set forth in the product literature should be strictly observed.

Consult literature and dosage instructions, available on request, before prescribing.

*Selected bibliography from 36 published papers: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, *Virginia M. Month.*, 87:23, 1960. 4. G. C. Griffith, *Clin. Med.*, 6:1555, 1959. 5. G. C. Griffith, *Dis. Nerv. System*, 21:(Suppl.), 101, 1960. 6. L. Alexander and S. R. Lipsett, *Dis. Nerv. System*, 20:(Suppl.), 26, 1959.*

MARPLAN® = 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine



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Division of Hoffmann-La Roche Inc.

Highly opaque water-soluble contrast medium for

GASTROENTERIC RADIOGRAPHY



ORAL New Hypaque[®] SODIUM POWDER AND LIQUID

- Highly versatile—any concentration can be prepared readily (One level measuring spoon of powder contains 10 Gm.)
- Excellent mucosal outline
- No danger of obstruction
- Miscible with blood
- Virtually innocuous if spilled through perforation

Winthrop
LABORATORIES
New York 10, N. Y.

Hypaque sodium, brand
of diatrizoate sodium

HOW SUPPLIED: Powder: 250 Gm.
Liquid: 50 Gm. (120 cc.)



to prevent pain and anxiety in angina

For your angina patients, EQUANITRATE helps control pain and angina-triggering anxiety. EQUANITRATE reduces the number and severity of attacks, increases exercise tolerance, and lessens nitroglycerine dependence. Russek† reports "The best results . . . in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE] in the patients studied."

For further information on the limitations, administration, and prescribing of EQUANITRATE, see descriptive literature or current direction circular.

†Russek, H.I.: *Am J. Cardiol.* 3:547 (April) 1959.

Supplied: EQUANITRATE 10 (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE 20 (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

Wyeth Laboratories Philadelphia 1, Pa.



Equanitrate®

Meprobamate and Pentaerythritol Tetranitrate, Wyeth



When Peridial is used the peritoneum becomes a dialyzing membrane through which filterable poisons or wastes are drawn into the Peridial solution and removed. The danger of contamination and risk of infection is greatly reduced by the specially designed closed system of infusion and drainage. Peridial flows through a special catheter into the peritoneal cavity. At the end of an hour, the Peridial solution is drained by gravity back into the original bottles without any break in sterile technique. This drawing off into the same bottles with the fluid line marked also permits accurate determination of the amount of fluid removed. As soon as the peritoneal cavity is empty, fresh Peridial solution is introduced with a new administration set.

This effective, practical, readily available medical procedure has been successfully used in treatment of acute renal failure, barbiturate poisoning, intractable edema, hepatic coma, hypercalcemia and chronic uremia, and has been reported useful in acute methyl alcohol poisoning.*

Available in 1 liter flasks with administration sets and catheter. Peridial with 1½% dextrose / Peridial with 7% dextrose

**FOR
PERITONEAL
DIALYSIS**

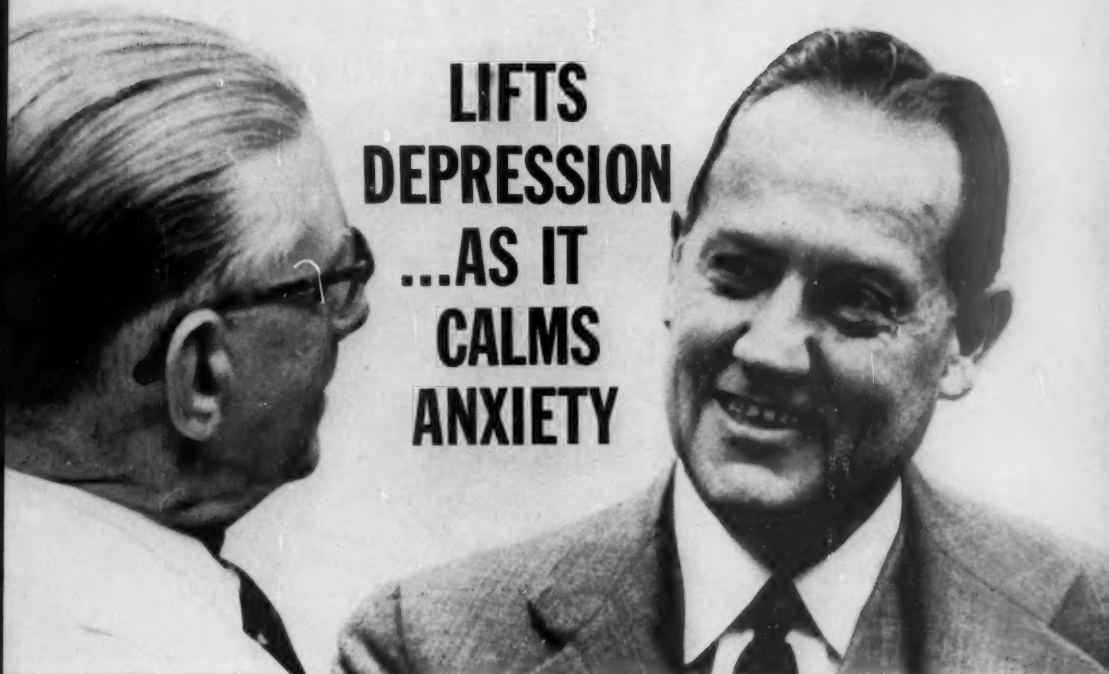
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**Stinebaugh, B. J.: A.M.A. Arch.
Int. Med. 105:613, 1960.*

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LIFTS DEPRESSION ...AS IT CALMS ANXIETY

Thanks to your balanced Deprol therapy... his depression has lifted and his mood has brightened up - while his anxiety and tension have been calmed down. He sleeps better, eats properly, and normal drive and interest have replaced his emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient - they often aggravate anxiety and tension.

And although amphetamine-barbiturate combinations may counteract excessive stimulation - they often deepen depression and emotional fatigue.

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety - a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly - you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly - often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Compatible with therapy for physical diseases. Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver toxicity, hypotension or tachycardia.

▲Deprol®

Dosage: Usual starting dose is 1 tablet a.i.d. When necessary, this may be gradually increased up to 3 tablets a.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.



WALLACE LABORATORIES / Cranbury, N. J.

CO-4531

IN AGITATION AND APPREHENSION...

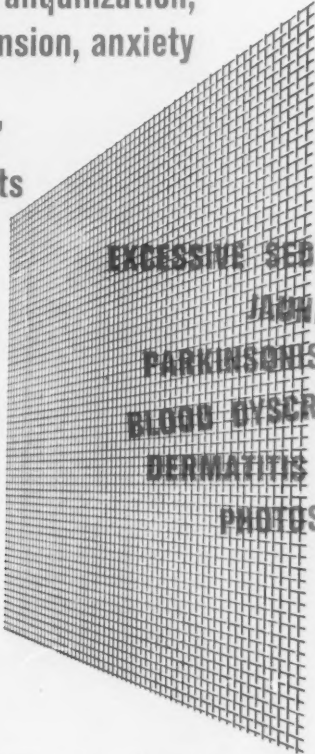


Mellaril[®]

THIORIDAZINE HCl

provides highly effective tranquilization,
relieves agitation, apprehension, anxiety

and "screens out"
certain side effects
of tranquilizers,
making it
virtually free of:



EXCESSIVE SEDATION
JAUNDICE
PARKINSONISM
BLOOD DYSCRASIA
DERMATITIS
PHOTOSENSITIVITY

"The side-effects which we have observed during trials with Mellaril have not been of a serious nature and we believe that the claim can justly be made that Mellaril has fewer side-effects than any other of the phenothiazine compounds."¹

In Agitation, Anxiety and Tension "The literature is replete with references to the phenothiazines and the role they play in the treatment of tension states, anxiety, and agitation. While numerous compounds have been introduced, the search continues for an ataraxic that is not only effective, but is relatively free of annoying side effects. My experience with thioridazine [Mellaril] in 87 patients confirms the findings of other investigators regarding its efficacy in the control and treatment of various nervous and mental disturbances seen in everyday practice. Also, it does not induce parkinsonism, blood dyscrasia or liver damage."²

Mellaril is indicated for varying degrees of agitation, apprehension, and anxiety in both ambulatory and hospitalized patients.

Usual starting dose: Non-psychotic patients — 10 or 25 mg. t.i.d.; Psychotic patients — 100 mg. t.i.d.

Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

1. Sandison, R. A., Whitelaw, E., and Frier, J. D. C.: Clinical trials with Mellaril in the treatment of schizophrenia, *Journal of Mental Science* (British Journal of Psychiatry) 106:732, April, 1960. 2. Freed, S. C.: Thioridazine, a neuroleptic in general practice, *International Record of Medicine*, 172:644, Oct. 1959.




NEW to aid relief of all 3—

 **tension**

 **spasm**

 **stasis**

in functional G.I. disturbances

 **DECHOLIN-BB[®]**
(Hydrocholeretic • Antispasmodic • Sedative, AMES)

DECHOLIN-BB combines three components whose predictable effect and complementary action are well established. DECHOLIN-BB is indicated as an adjunct in the management of chronic constipation, nervous indigestion, indigestion of pregnancy, and irritable colon with constipation associated with emotional tension, smooth-muscle spasm and biliary/intestinal stasis.

tension

Sedation with butabarbital helps relieve the emotional tension and anxiety-induced nervous hyperactivity which is a basic cause of functional G.I. disturbances.

spasm

Spasmolysis with belladonna suppresses G.I. hypersecretion and smooth-muscle hyperactivity, relaxes G.I. and biliary sphincteric spasm, and helps insure unimpeded bile flow.

stasis

Hydrocholeresis with DECHOLIN[®] improves biliary function and intestinal motility, and hydrates bowel contents, by markedly increasing volume and water content of bile.

Each DECHOLIN-BB tablet contains: butabarbital sodium, 15 mg. ($\frac{1}{4}$ gr.); DECHOLIN[®] (dehydrocholic acid, AMES), 250 mg. ($3\frac{3}{4}$ gr.); belladonna extract (total alkaloids, 0.125 mg.), 10 mg. ($\frac{1}{8}$ gr.).

Average adult dose: 1 or, if necessary, 2 tablets three times daily. **Contraindications:** Biliary tract obstruction, acute hepatitis and glaucoma. **Precautions:** Patients receiving DECHOLIN-BB should be examined periodically for increased intraocular pressure or signs of barbiturate habituation or addiction during long-term use. Drivers should be cautioned against possible risk of drowsiness. **Available:** DECHOLIN-BB, bottles of 100.

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AMES
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Elkhart • Indiana
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Arrest the Coughs that Steal Sleep...

CHRONIC SINUSITIS
PHARYNGITIS
INFLUENZA-COLDS
BRONCHITIS
CHRONIC LUNG DISEASE
CARDIAC DECOMPENSATION
MEASLES



Prescribe

TUSSIONEX[®]

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

8-12 Hour Cough Control with a Single Dose

- Permits Natural Discharge of Mucus
- Predictable Antitussive Action with Minimum Amount of Narcotic through 'Strasionic' Release

TWO FORMS: Tussionex Thixaire™ Suspension • Tussionex Tablets

Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Dose: 1 teaspoonful or tablet q 12h. Children under 1 year, ¼ teaspoonful q 12h; 1-5 years, ½ teaspoonful q 12h.

Rx only. Class B taxable narcotic.

Tussionex—made and marketed only by

STRASENBURGH

Her hunger



is "liquidated"... but her appetite survives!

Mealtime *hunger* reflects a physiological need quickly satisfied by food—liquid or solid.

But *appetite* represents a psychological need which is often the obese patient's biggest problem. Measures that satisfy hunger alone are not enough. Mealtimes rapidly become tedious on unnatural diets... and high caloric snacks, between-meal nibbling, and refrigerator raiding provide an appetizing consolation! When appetite survives, willpower soon vanishes.

You can help her *satisfy* her *appetite* as well as her hunger... and still be sure of

SUSTAINED WEIGHT CONTROL

by prescribing Biphedamine or Ionamin. A single capsule dose appeases appetite for 10-14 hours. Your patient enjoys normal food (in lesser quantities) while better eating habits and proper weight are gradually established and maintained.

If She's "Sedentary"

BIPHETAMINE®
A "STRABONIC" ANORETIC RESIN

BIPHETAMINE '20'
(20 mg.)

BIPHETAMINE '12½' **BIPHETAMINE '7½'**
(12.5 mg.) (7.5 mg.)

Each capsule of each strength contains equal parts of d-amphetamine and dl-amphetamine as cation exchange resin complexes of sulfonated polystyrene.

If She's "Active"

IONAMIN®
A "STRABONIC" ANORETIC PHENTERMINE RESIN

IONAMIN '30'
(30 mg.)

IONAMIN '15'
(15 mg.)

Each capsule of each strength contains phentermine as a cation exchange resin complex of sulfonated polystyrene.

If She's "Refractory"

NEW BIPHETAMINE-T
A "STRABONIC" ANORETIC RESIN

BIPHETAMINE-T '20' **BIPHETAMINE-T '12½'**

Each capsule of each strength contains Tuazole® and equal parts of d-amphetamine and dl-amphetamine—all as cation exchange resin complexes of sulfonated polystyrene.

Single Capsule Daily Dose 10 to 14 hours before retiring

STRASENBURGH

AKALON-T[®]

'STRASIONIC' ANTICHOLINERGIC

METHSCOPOLAMINE-TUAZOLE[®] RESIN

**A single
capsule dose

CALMS
THE GI TRACT

COMBATS
EXCESSIVE
GASTRIC SECRETIONS

for

8-12 HOURS**

*'Strasionic' release makes
the BIG difference*



TWO STRENGTHS



AKALON-T '5': 5 mg. Methscopolamine and 20 mg. Tuazole (Brand of 2-methyl-3-orthotolyl-quinazalone) as cation exchange resin complexes of sulfonated polystyrene.

Rx Only



AKALON-T '10': 10 mg. Methscopolamine and 40 mg. Tuazole (Brand of 2-methyl-3-orthotolyl-quinazalone) as cation exchange resin complexes of sulfonated polystyrene.

Akalon-T—made and marketed ONLY by **STRASENBURGH**

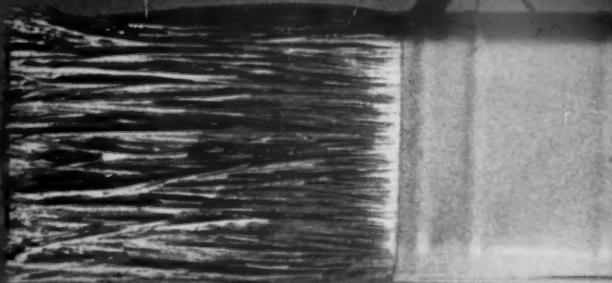
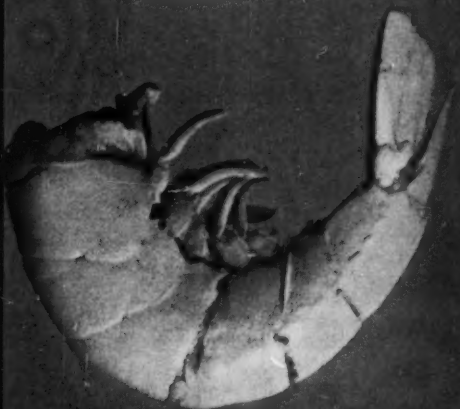
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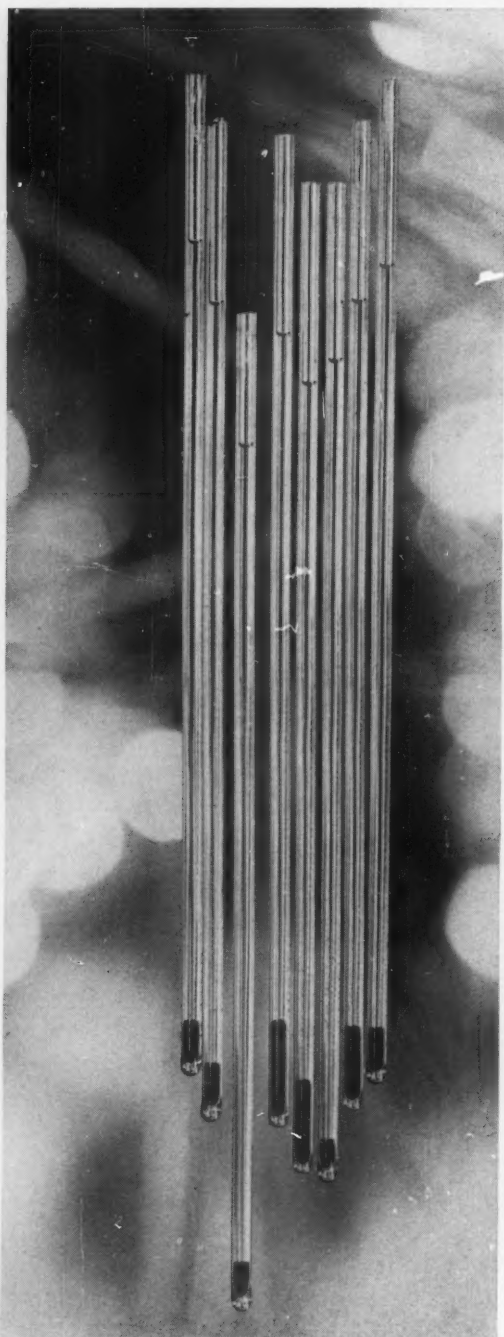
checks
"runaway"
allergic
reactions

METRETON[®]
corticoid-antihistamine compound TABLETS

For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.

S-969





IMMUNOCRIT® tubes, pictured here 4 times actual size, show results of centrifuging patients' serums with BETA-L TEST antiserum. Longest columns of precipitate indicate high beta-lipoprotein levels.

NEW...
A SPECIFIC
SIMPLE
INEXPENSIVE
TEST FOR
ESTIMATING SERUM
BETA-LIPOPROTEIN
LEVELS
BETA-L TEST™

The growing evidence implicating beta-lipoprotein as one of the agents responsible for atherosclerosis has emphasized the need for a test procedure which is reliable, yet simple enough to be suited to clinical purposes.¹ Hyland BETA-L TEST answers this need. BETA-L TEST results show a close correlation with complex quantitative methods now in use, yet BETA-L TEST can be performed in ten minutes on one drop of serum and employs a minimum of laboratory equipment and technical skill.²

The resulting economy and simplicity provide you with a reliable routine screening test and make frequent serial determinations of beta-lipoprotein practical for the first time.

When ordering your next beta-lipoprotein determinations, specify Hyland BETA-L TEST. Materials for BETA-L TEST are now available to your laboratory in 60-test kits.

1. Wood, F. C., Gurin, S., and Kuo, P. T.: Medical Correlation Clinic on Atherosclerosis and Coronary Artery Disease, *Am. Pract.-Dig. Treat.* 12: 235 (April) 1961.

2. Heiskell, C. L., Fisk, R. T., Florsheim, W. H., Yachi, A., Goodman, J. R., and Carpenter, C. M.: A Simple Method for Quantitation of Serum Beta-Lipoproteins by Means of the Immunocrit, *Amer. J. Clin. Path.* 35: 222 (March) 1961.



HYLAND LABORATORIES

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Branch Office: 160 Lockwood Ave., Yonkers, N.Y.

a pair of gynecologic patients:



both are free of pain—but only one is on

DILAUDID®

(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia before and after gynecologic, obstetric and surgical procedures. Its high therapeutic ratio is commonly reflected by lack of nausea and vomiting — and marked freedom from dizziness, somnolence, anorexia and constipation.

▲ **by mouth** ▲ **by needle** ▲ **by rectum**

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.



KNOLL PHARMACEUTICAL COMPANY • ORANGE, NEW JERSEY

IN PEPTIC ULCER AND HYPERACIDITY
with associated TENSION and NERVOUSNESS

NACTISOL*

- suppresses gastric acid secretion at the parietal cell level
- decreases gastrointestinal hypermotility
- relieves nervousness and tension

NACTISOL combines:

NACTON® 4 mg. new inhibitor of gastric acid secretion and hypermotility
polidine methylsulfate "...reduces the total output of gastric HCl by about 60%"¹
plus

BUTISOL SODIUM® 15 mg. "daytime sedative" with highest therapeutic
butabarbital sodium index² (highly effective, minimal side effects)

- Side effects with NACTISOL therapy have been minimal.³⁻⁵

NACTISOL*...in scored, yellow tablets



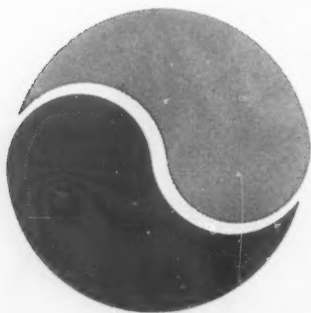
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2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, *Postgrad. Med.* 26:502-509 (October) 1959.
3. Steigmann, F.: Clinical Report to McNeil Laboratories.
4. Lorber, S. H.: Clinical Report to McNeil Laboratories, December 6, 1960.
5. Rider, J. A.: Clinical Report to McNeil Laboratories.

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essential
partners
in the
control
of edema

classic
MERCUHYDRIN[®]
brand of meralluride sodium
nonmercurial
METAHYDRIN[®]
brand of trichlormethiazide

*Now...*the alternate or combined use of these two drugs
can help the physician meet with maximum efficiency
the demands of diuretic therapy in almost any phase or degree
of cardiac edema—acute or chronic.

SEND FOR METAHYDRIN[®] BROCHURE

SUPPLIED:

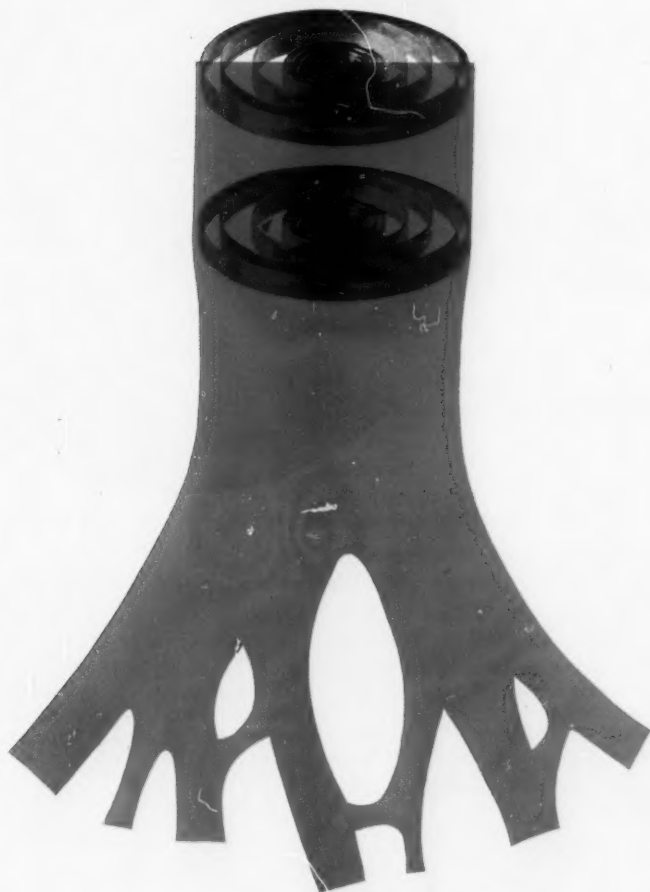
METAHYDRIN—Tablets of 2 mg. and 4 mg. in bottles of 100 and 1000.

MERCUHYDRIN—1 cc. and 2 cc. ampuls in boxes of 12, 25 and 100,
and 10 cc. rubber capped, multiple dose vials in
boxes of 6, 25 and 100.
Needs no refrigeration.

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Hygroton®
brand of chlorthalidone
**in hypertension and edema,
longer in action
smoother in effect**



Longer action¹ provides smooth, evenly-sustained therapeutic effect.² ■ Potent antihypertensive properties facilitate effective treatment of hypertension, frequently without auxiliary agents.³ ■ Safeguards against significant potassium loss.⁴ ■ Intensity of saluretic action enables liberalization of dietary salt restriction.³ ■ Simplified dosage schedule affords economy of maintenance on just 3 doses per week.²

References: 1. Ford, R. V.: Current Therap. Research 2:347, 1960. 2. Fuchs, M., and others: Current Therap. Research 2:11, 1960. 3. Ford, R. V.: Connecticut Med. 24:704-707, (Nov.) 1960. 4. Ford, R. V.: Texas State J. Med. 56:343, 1960. Detailed literature available on request.

Hygroton®, brand of chlorthalidone, is available as white, single-scored tablets of 100 mg.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York



HY573-61

Geigy

NEW
comprehensive
digestant
with the
most
potent
enzyme
available
for
digestion of



—also unsurpassed potency for digestion of starch, protein and cellulose

- the *only* digestant with Lipancreatin,* proven superior to Pancreatin N.F.
- the *only* digestant with fat-splitting lipase activity 12 times as great as that of Pancreatin N.F.

When the question is digestion because of your patient's inability to handle fat, starch, protein or cellulose, you can provide dependable relief with COTAZYM-B, which contains the essential pancreatic enzymes lipase, trypsin and amylase, plus bile salts and cellulase. A daily dose of 6 COTAZYM-B tablets is sufficient to emulsify and digest 50 Gm. of dietary fat, and to digest all of the protein and starch in a typical diet (100 Gm. protein, 250 Gm. starch) and 480 mg. cellulose.

Dosage: 1 or 2 tablets with water just before each meal.

Supply: Bottles of 48 tablets.

Write for samples and comprehensive literature.

NEW **Cotazym-B**
Lippancreatin Bile Salts Cellulase

ORGANON INC., West Orange, New Jersey



**The Significance of Lipancreatin (Pancreatic Enzymes Concentrated 'Organon')*

A product of original Organon research, lipancreatin provides for the first time in digestant preparations a known, constant amount of fat-digesting lipase in addition to trypsin and amylase. It surpasses in assayable digestive activity all presently available pancreatin preparations.

Clinically Proven
in more than 750 published clinical studies
and over six years of clinical use

Outstandingly Safe and Effective

for the tense and
nervous patient



- 1 simple dosage schedule relieves anxiety dependably — without the unknown dangers of "new and different" drugs
- 2 does not produce ataxia, stimulate the appetite or alter sexual function
- 3 no cumulative effects in long-term therapy
- 4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- 5 does not muddle the mind or affect normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS®—400 mg. unmarked, coated tablets; and in sustained-release capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).

*TRADE-MARK

Miltown®
meprobamate (Wallace)

 WALLACE LABORATORIES / Cranbury, N. J.

CM-4751

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in the wide middle region of pain

Percodan

(Salts of Dihydro- dihydrocodeinone and Homatropine, plus APC)

TABLETS

fills the gap
between
mild oral and
potent
parenteral
analgesics¹⁻⁷

- acts in 5-15 minutes
- relief usually lasts 6 hours or longer
- toleration excellent... constipation rare
- sleep uninterrupted by pain

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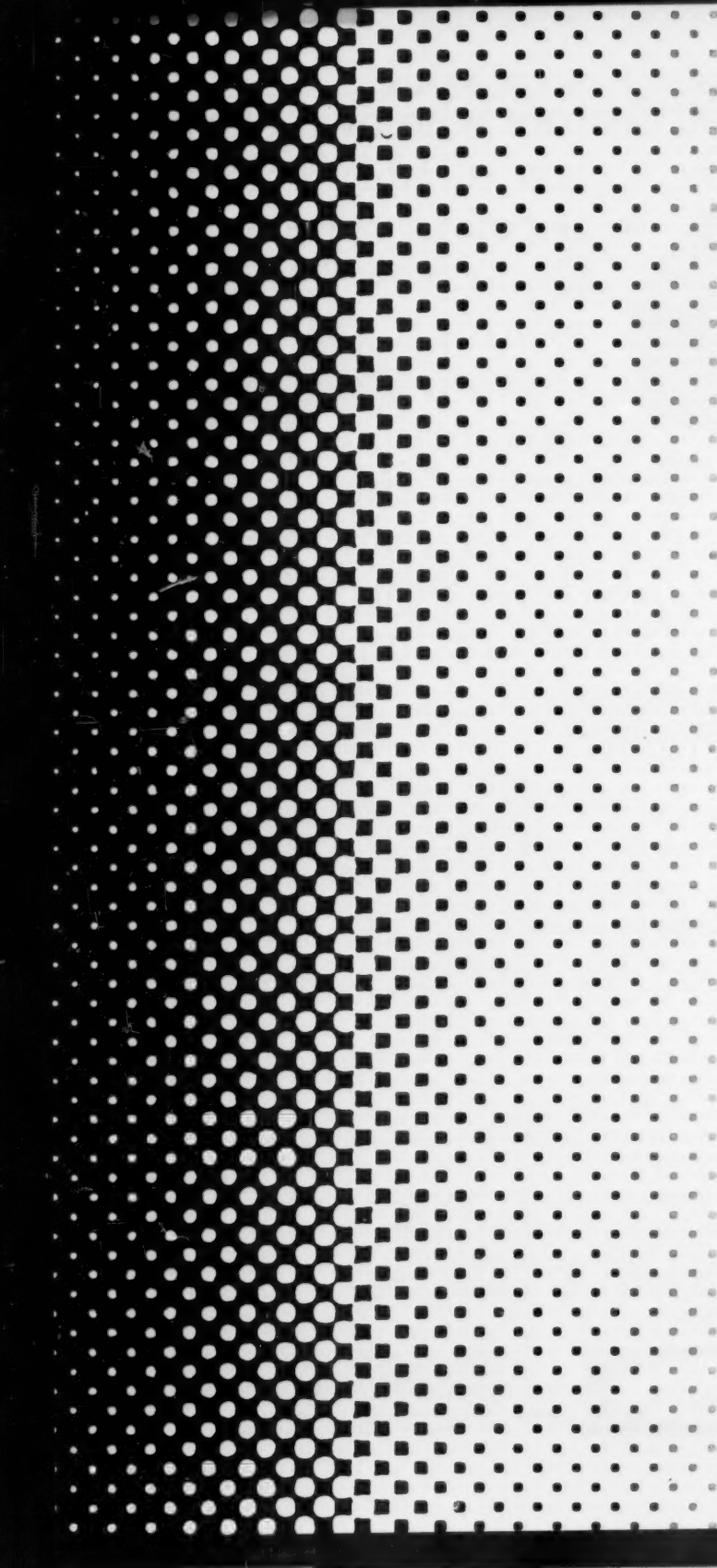
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1. Blank, P., and Boas, H.: Improved analgesia for moderate pain. *Ann. West. Med. & Surg.* 6:376, 1952.
2. Bonica, J. J., et al.: The management of postpartum pain with dihydrohydroxycodeinone (Percodan). Evaluation with codeine and placebo. *West. J. Surg.* 85:84, 1957.
3. Cass, L. J., and Frederick, W. S.: A controlled study in pain relief. *M. Times* 84:1318, 1956.
4. Chasko, W. J.: Pain-free dental surgery: Postoperative extension of the pain-free state. *J. District of Columbia Dent. Soc.* 31:3, No. 5, 1956.
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7. Piper, C. E., and Nicklas, F. W.: Percodan for pain in industrial practice. *Indust. Med.* 23:510, 1954; abstracted, *Clin. Med.* 3:1008, 1956; *Current M. Digest* 22:135, No. 3, 1955.



a spreading pattern of therapeutic success

A rewarding approach to the emotional and somatic manifestations of anxiety, agitation and tension, Librium therapy is now being utilized in many different areas of general practice. Approximately 3.5 million Librium-treated cases, as well as more than 70 published reports, offer testimony to this spreading pattern of therapeutic success. They corroborate observations, gained over a span of more than three years, that Librium is pharmacologically and clinically in a class by itself.

Librium has been found of value in alleviating anxiety and tension associated with:

- emotional disturbances
- personality disorders
- cardiovascular conditions
- gastrointestinal disorders
- gynecologic disorders
- dermatologic conditions
- psychiatric disorders

Consult literature and dosage information, available on request, before prescribing.

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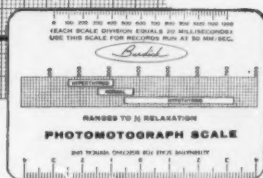
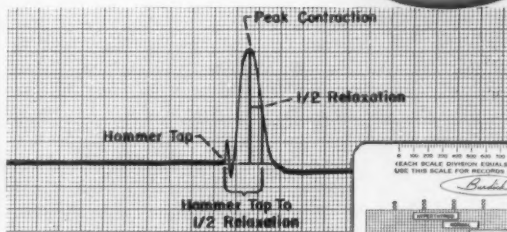
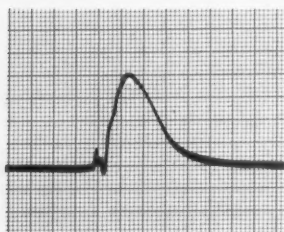
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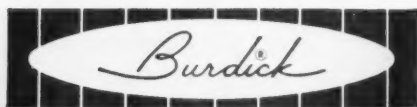
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■ enhanced anti-inflammatory, antiallergic, antipruritic effects ■ far less gastrointestinal distress ■ may be of value when other corticoids have failed ■ virtually no mood changes, edema, sodium or water retention, or secondary hypertension

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*Glaser, J.: Ann. Allergy 10:150 (May) 1960.

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The enhanced POTABA + 6® is indicated in the treatment of scleroderma and other entities involving fibrosis. The significant antifibrosis action of POTABA® (Potassium p-Aminobenzoate, Glenwood) is here combined with Pyridoxine to help replenish the depleted stores of this essential vitamin in subjects with scleroderma.



In a series of 72 cases of scleroderma ⁽¹⁾ 60 patients continued on POTABA for more than 3 months, and 58 of these had moderate to marked improvement, for a 97 PER CENT RESPONSE. There was no selection of the patients admitted to this series, each being placed on the program regardless of the severity of the disease ⁽¹⁾.

1. Zarafonitis, Chris J. D.: Treatment of Scleroderma, *Annals of Int. Med.*, 50:343-365 (1959)

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IN BRIEF

ATARAXOID contains the glucocorticoid prednisolone and the ataractic agent, hydroxyzine.

ADVANTAGES: ATARAXOID combines the tension-relieving effects of hydroxyzine with the anti-inflammatory action of prednisolone, a well-established corticosteroid, for superior control of the signs and symptoms of rheumatoid arthritis without unexpected side effects. An important result of the therapeutic effects of ATARAXOID is noted by Warter*: "In addition it was possible in many cases for the first time to gain the active cooperation of patients in the management of their disease."

INDICATIONS: Rheumatoid arthritis; other collagen diseases and related conditions; other musculoskeletal disorders (myositis, fibrositis, bursitis, etc.); allergic states, including chronic bronchial asthma and severe hay fever; and allergic/inflammatory diseases of the skin and eyes.

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SIDE EFFECTS: Prednisolone may produce all of the side effects common to other corticosteroids. As with other corticosteroids, insomnia, mild hirsutism, moonface and sodium retention have occurred. Osteoporosis may develop after long-term corticosteroid therapy.

PRECAUTIONS AND CONTRAINDICATIONS: Usual corticosteroid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of diabetic patients and patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered.

SUPPLIED: As green, scored ATARAXOID 5.0 Tablets, containing 5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride and blue, scored ATARAXOID 2.5 Tablets, containing 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride.

More detailed professional information available on request.

*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, *J. M. Soc. New Jersey* 54:7, 1957.

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ARTHRITIS RELIEVE BOTH THE
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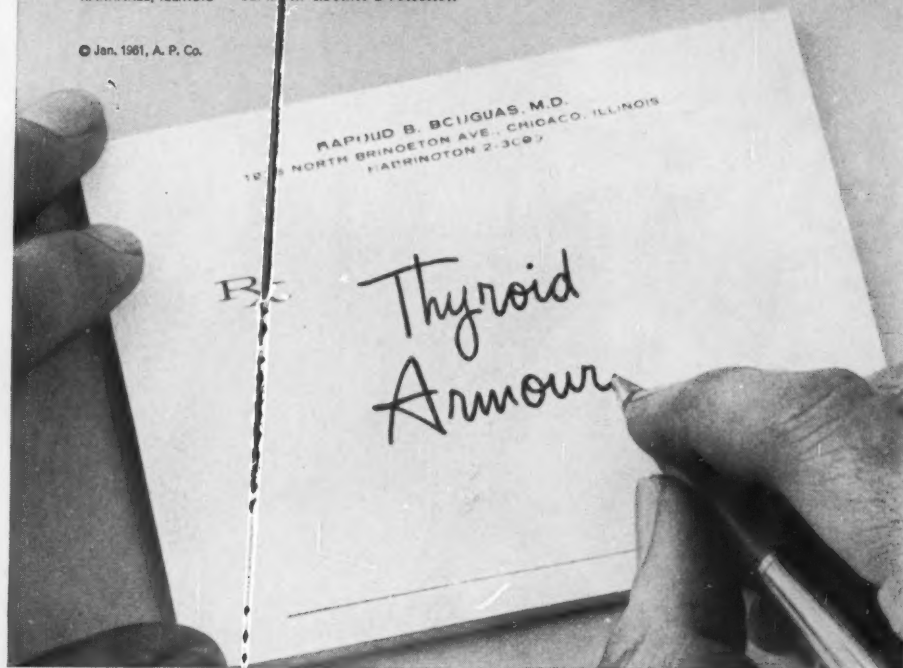
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THYROID U.S.P.

Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. **USES:** Thyroid deficiencies, cretinism, myxedema, nodular goiter (nontoxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved, i.e., gynecologic conditions such as functional menstrual disorders, sterility, habitual abortion; recurring conjunctivitis; certain types of anemias and obesity; and certain changes which occur in hair, skin and fingernails. **DOSAGE:** $\frac{1}{4}$ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. **CONTRAINDICATIONS:** Heart disease and hypertension, unless the metabolic rate is low. **SUPPLIED:** Tablets—bottles of 100, 1000 and larger; potencies of $\frac{1}{4}$, $\frac{1}{2}$, 1, 2 and 5 grains. Powder—1 oz. 4 oz., and 1 lb. bottles.



*when emotions interfere
with medical management*

**or
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of tried, proved, effective
WYETH ataractic
agents for flexible
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relaxes the tense, anxious patient

Now Wyeth announces a new, continuous release dosage form of meprobamate—EQUANIL L-A Capsules. An easy-to-follow b.i.d. dosage regimen provides your patients with uninterrupted drug action for prolonged periods.

EQUANIL is a preferred agent for treating anxiety and tension; predictable in action, well tolerated.

Indicated for your patients displaying mild to moderate emotional and physical problems, which are expressed as:

- simple anxiety
- a symptom complex accompanying medical disorders and surgical procedures
- muscle spasm, as in musculoskeletal disorders such as rheumatic conditions

No ataxia, extrapyramidal symptoms, undue sedation, or significant effect upon mental or physical performance.



NEW

convenient,

long-acting dosage form

Equanil L-A

CAPSULES



Detailed Information on

NEW EQUANIL® and EQUANIL® L-A

Meprobamate, Wyeth

EQUANIL has been proved effective as a skeletal muscle relaxant and in the management of anxiety and tension occurring either alone or as an accompanying symptom complex to medical disorders. Although not a hypnotic, EQUANIL fosters normal sleep through both its antianxiety and muscle-relaxant properties.

EQUANIL is beneficial in relieving anxiety and emotional stress in the psychosomatic disorders—allergy, dermatoses, cardiovascular and hypertensive disease, gastrointestinal disorders, and tension headache.

Directions: Initial and usual adult dose of EQUANIL is 400 mg., given 3 or 4 times daily. This will usually be sufficient in the management of simple anxiety and tension or, adjunctively, in anxiety and tension complicating medical disorders and surgical procedures. Doses above 2400 mg. daily are not recommended, even though higher doses have been used by some investigators. Elderly patients usually tolerate EQUANIL well.

In children 3 years of age and older, the initial dosage is 100 to 200 mg. 2 or 3 times a day. Dosage may be increased as necessary, daily dosage of 2.4 Gm. being well tolerated by older children. Infants with cerebral palsy have been given EQUANIL from 3 months of age in daily doses of 125 to 400 mg.

NEW EQUANIL L-A

EQUANIL L-A capsules, 400 mg., may be given twice daily where prolonged effects are required and ease of administration is desirable. The average adult daily dose is 1 capsule twice a day although a dosage range up to two capsules twice a day may be required by certain patients.

Important: Careful supervision of dose and amount prescribed is advised, especially for patients with a known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons (alcoholics, former addicts, and other severe psychoneurotics) has been reported to result in dependence on the drug. Where excessive dosage has been continued for weeks or months, dosage should be reduced gradually rather than abruptly, since withdrawal of a "crutch" may precipitate withdrawal reactions of greater proportions than those for which the drug was originally prescribed. Abrupt discontinuance of doses in excess of the recommended dose has occasionally resulted in epileptiform seizures.

Special care should be taken to warn patients taking meprobamate that their tolerance to alcohol may be lowered with resultant slowing of reaction time and impairment of judgment and coordination.

Precautions: Serious side effects have rarely been encountered following the administration of EQUANIL. Drowsiness may occur, particularly early in the course of EQUANIL therapy, but, as a rule, disappears as therapy is continued. Should drowsiness persist, it can usually be controlled by decreasing the dose; occasionally it may be desirable to administer central stimulants such as amphetamine or mephentermine sulfate (WYAMINE® Sulfate, Wyeth), concomitantly with EQUANIL.

The only serious side effects reported to attend use of meprobamate are rarely encountered allergic reactions. Such response is developed, as a rule, in patients who have had only 1 to 4 doses of meprobamate and have not had previous contact with the drug. Previous history of allergy does not appear to be related to the incidence of reactions.

Mild reactions are characterized by an itchy urticarial or erythematous, maculopapular rash, which may be generalized or confined to the groins. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have also been reported.

More severe cases, observed only very rarely, may also have fever, fainting spells, angioneurotic edema and bronchial spasms. Treatment consists of the administration of epinephrine, antihistamine and, possibly, hydrocortisone. EQUANIL should be stopped and reinstitution of therapy should not be attempted.

For further information on prescribing and administering EQUANIL and EQUANIL L-A, see descriptive literature, available on request.

Wyeth Laboratories Philadelphia 1, Pa.

calms the moderately disturbed patient

PROZINE reduces motor excitability, apprehension, agitation, anxiety and tension. It is for patients in the middle range of the spectrum of emotional disturbances. For the patient who has not responded satisfactorily to meprobamate.

Indicated for your patients displaying moderate to moderately severe emotional problems resulting in anxiety expressed as:

- abnormal behavior in children, adolescents, and senile patients
- secondary reactions to acute or chronic disease
- moderate to severe psychoneuroses
- somatic disorders such as headache, vertigo, nausea and vomiting, muscle spasm, insomnia
- mild psychoses



PROZINE

WITH NEW HALF-STRENGTH CAPSULES

titration of dosage can be accomplished easily. The halved-dose of PROZINE is especially useful with patients who experience undue drowsiness on full dosage during the initial therapy period of 72 hours or who require lesser amounts of PROZINE for maintenance therapy.



Detailed Information on

PROZINE®

Meprobamate and Promazine Hydrochloride, Wyeth

FULL-STRENGTH AND NEW HALF-STRENGTH

PROZINE is indicated in the management of: (1) primary organic disease with emotional overlay of anxiety, tension, apprehension, and agitation: these symptoms are often observed in conjunction with peptic ulcer, gastrointestinal tension states, cardiovascular disease, hypertension, dermatitis, allergic rhinitis, arthritis, carcinoma, tuberculosis, premenstrual tension, muscular spasm and injury; (2) gastrointestinal disturbances, nausea, and vomiting associated with emotional stress; (3) chronic alcoholism; (4) functional emotional problems associated with marked anxiety, apprehension, tension headaches, vertigo and muscle spasm; (5) behavioral problems in children, adolescents and senility; (6) behavioral disorders associated with psychotic illness, manifest by such symptoms as belligerence, confusion, delusions, insomnia, hyperactivity, fear and depression; (7) nighttime sedation; and (8) depression associated with anxiety and tension.

Directions: The usual dosage is 1 or 2 full-strength capsules, 3 or 4 times daily. For nighttime sedation, 2 capsules. If drowsiness is troublesome in the first 72 hours of treatment, a reduction of dosage may be indicated.

NEW HALF-STRENGTH CAPSULES

In patients unduly responsive to PROZINE, doses of 1 to 2 half-strength capsules 2 or 3 times a day may be indicated.

Promazine enhances analgesics and central nervous system depressants, and such agents, when required, should be given in reduced doses.

Precautions: The incidence of agranulocytosis with promazine is less than 0.001%, and usually has been observed only in patients who have taken high doses of promazine for prolonged periods. However, symptoms of fever and sore throat should be reported and diagnosis confirmed by white blood cell count and differential smears. Intermittent hematological examinations should be made on all patients taking PROZINE for prolonged periods. Excessive and prolonged use of meprobamate in susceptible persons (alcoholics, former addicts, and other severe psychoneurotics) has been reported to result in dependence on the drug. In such cases, reduce dosage gradually to avoid withdrawal reactions and possible epileptiform seizures. Gross overdosage of PROZINE may result in hypotension. When a sympathomimetic agent is indicated, norepinephrine is recommended, since promazine reverses the effect of epinephrine. In cases of allergic reactions, PROZINE should be discontinued. It has been reported that patients may develop hepatic dysfunction when taking promazine if chlorpromazine had previously been given. This reaction may occur even though not evident during chlorpromazine therapy. Seizures, reported as occurring during promazine therapy, occur usually only with rapid large increases in dose to levels greater than 1 Gm. daily, or when the patient has a history of epilepsy inadequately controlled with anticonvulsant therapy.

Contraindications: Do not use PROZINE in comatose states caused by alcohol, barbiturates, opiates, etc., or when a drop in blood pressure is undesirable.

For further information on prescribing and administering PROZINE, see descriptive literature, available on request.

Wyeth Laboratories Philadelphia 1, Pa.

controls the acutely agitated patient

SPARINE is a versatile agent for the control of acute manifestations of severe mental and emotional disturbances.

Indicated for the prompt management of your patients displaying:

- central nervous system excitation, apprehension, or acute agitation
- postalcoholic syndrome, including delirium tremens and acute hallucinosis
- symptoms of drug withdrawal
- anxiety, pain, nausea, vomiting, hiccups during medical emergencies

With SPARINE in your bag, you are always prepared to cope with emergencies such as acute alcoholism and severe emotional disturbances. Useful in maintaining control.



Sparine

HYDROCHLORIDE

INJECTION

TABLETS

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Detailed Information on

SPARINE®

HYDROCHLORIDE

Promazine Hydrochloride, Wyeth

SPARINE effectively controls central nervous system excitation, allays apprehension and anxiety, calms the agitated patient and is a useful adjunct to the management of mental and emotional disturbances. It is effective in the management of alcohol-induced syndromes (delirium tremens, acute hallucinosis, acute tremulousness, inebriation) as well as the withdrawal symptoms of drug addiction. Both acute and chronic psychiatric illnesses respond to SPARINE therapy. SPARINE has been found to be useful in the management of nausea and vomiting of either central nervous system or gastric reflex origin. SPARINE effectively facilitates the action of analgesics and central nervous system depressants. It has been used as an adjunct to surgical sedation, allaying apprehension and reducing the dosage requirements for narcotics, analgesics and sedatives. SPARINE may be used as an aid in diagnostic and therapeutic regimens. Such non-specific symptoms as anxiety, pain, vomiting, nausea and hiccups frequently make more difficult both diagnosis and therapy of organic disease. SPARINE allays such symptoms without masking physical, neurological or laboratory findings.

Directions: For maximal therapeutic benefit the amount, route of administration and frequency of dose should be governed by the severity of the condition treated and the response of the patient. Oral administration should be used whenever possible; parenteral administration should be reserved for uncooperative patients or when nausea and vomiting interfere with oral administration. SPARINE when used intravenously should not exceed a concentration of 25 mg. per cc.; injection should be given slowly. Dilute 50 mg. per cc. concentration with equivalent volume of physiological saline before I.V. use. Avoid injection around or into the wall of the vein. Inject only into vessels previously undamaged by multiple injections or trauma.

In the management of acutely agitated patients, SPARINE should be given I.V. in initial doses of 50 to 150 mg. If the desired calming effect is not apparent within 5 to 10 minutes, additional doses up to a total of 300 mg. may be given. (In the acutely inebriated patient, the initial dose should not exceed 50 mg.) Once the desired effect is obtained, SPARINE may then be given I.M. or orally in maintenance doses of 10 to 200 mg. at four to six hour intervals. *In less severe disturbances, initial oral therapy may be satisfactory. When tablet medication is unsuitable or refused, SPARINE Syrup may be used.*

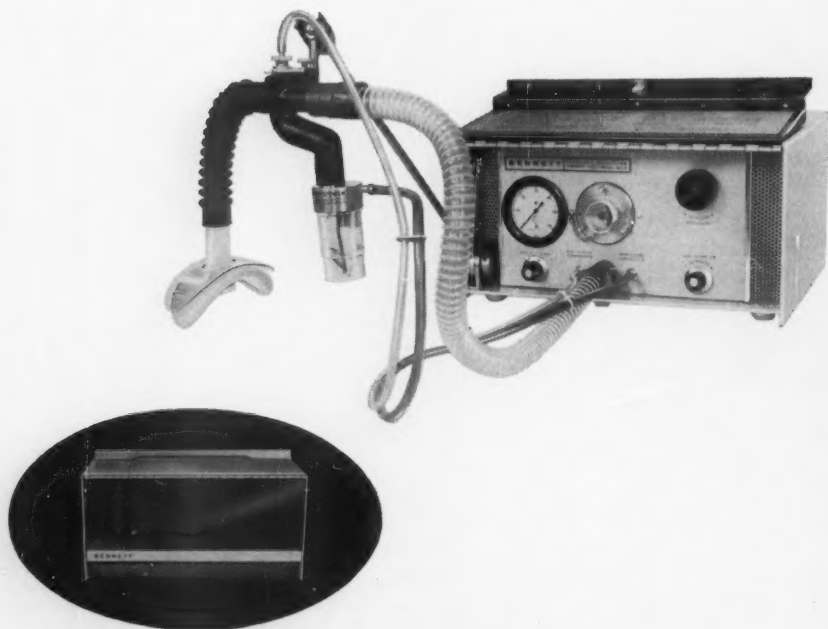
As an antiemetic, usual dose is 25 to 50 mg. repeated at four to six hour intervals. When oral route is not feasible, 50 mg. I.V. or I.M. will usually control the symptom, but oral medication should be initiated as soon as feasible. In medical emergencies, to allay apprehension and facilitate diagnosis or therapy, SPARINE should be given I.V., I.M. or orally in 50 to 200 mg. doses. See direction circular for details. In the management of pain associated with malignancy or chronic disease, SPARINE may be administered orally or I.M. in 25 to 50 mg. doses repeated at four to six hour intervals to allow for reduced dosage of analgesics.

Precautions: Although rare, drowsiness, dizziness and transitory postural hypotension may occur. If a vasopressor drug is indicated, norepinephrine is recommended, since SPARINE reverses the effect of epinephrine. Agranulocytosis has been reported in only 18 cases in about 3½ million patients. If, however, signs of cellular depression—sore throat, fever, malaise—become evident, discontinue SPARINE, check white blood cell count, and initiate antibiotic and other suitable therapy if indicated. Seizures, reported as occurring during SPARINE therapy, occur usually with rapid large increases in dose and at a daily dosage above 1 Gm. Caution must be exercised when administering SPARINE to patients with a history of epilepsy. There are reports in the literature indicating that patients may develop jaundice and/or liver dysfunction when taking promazine if they have previously taken chlorpromazine even though they did not show jaundice during chlorpromazine therapy. Avoid perivascular extravasation or intra-arterial injection, as severe chemical irritation or inflammatory response may result.

Because of its enhancing action on analgesics and central nervous system depressants, give them only in reduced dosage with SPARINE. Do not use in comatose states due to central nervous system depressants (alcohol, barbiturates, opiates, etc.). Use with caution in patients with cerebral arteriosclerosis, coronary heart disease, or other conditions where a drop in blood pressure may be undesirable.

For further information on prescribing and administering SPARINE, see descriptive literature, available on request.

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Model AP-4 is a new *portable* IPPB unit, employing the unique Bennett flow-sensitive valve. It is small, light, quiet in operation, and entirely self-contained. The controls are simple and straightforward. The unit delivers room air, with provision for optional oxygen enrichment through the nebulizer. It operates from 110V AC; or, by use of an accessory converter, from a car cigarette lighter.

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DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (1/4 gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
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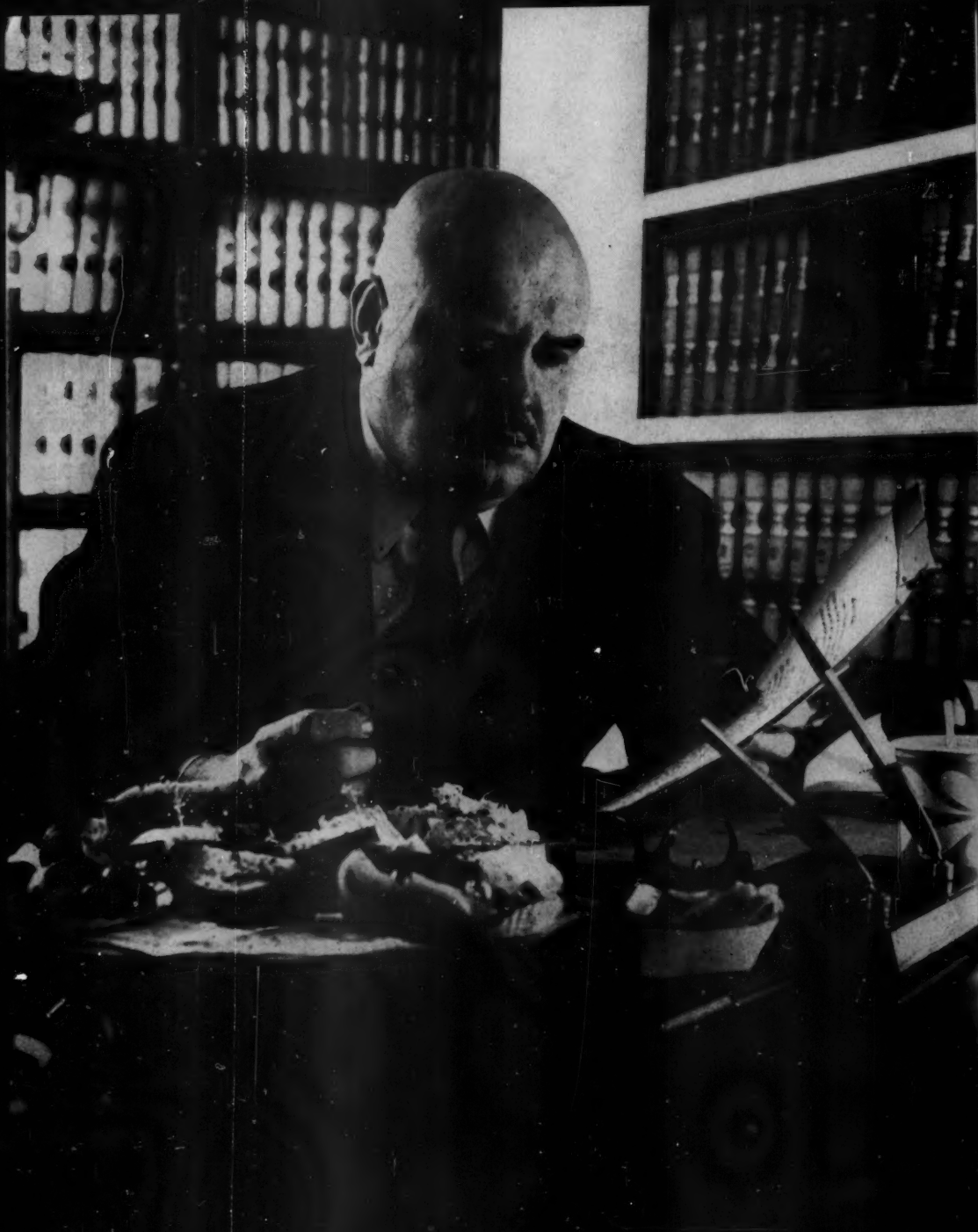
DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base 210 mg.) per 30 cc.

DONNAGEL plus powdered opium U.S.P. 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml.) This is the usual adult dose.

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for "special-problem" patients...when corticosteroid therapy is indicated

Aristocort

in rheumatoid arthritis

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ARISTOCORT Triamcinolone has long since proved its *unsurpassed efficacy and relative safety* in treating rheumatoid arthritis. Mounting clinical evidence has shown that ARISTOCORT is also highly valuable for the "special-problem" arthritic—the patient who, because of certain complications, was hitherto considered a poor candidate for corticosteroids.

for example:

SPECIAL PROBLEM: ANXIETY-TENSION

When triamcinolone was used, euphoria and psychic unrest rarely occurred. (McGavack, T. H.: *Clin. Med.* 6:997 [June] 1959.)

SPECIAL PROBLEM: OVERWEIGHT

No patient developed voracious appetite on triamcinolone. Preferable for the overweight person whose appetite is undesirably stimulated by other steroids. (Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 [June] 1958.)

SPECIAL PROBLEM: EDEMA

Since it does not produce edema, triamcinolone is useful in rheumatoid arthritis patients with cardiac decompensation who need steroid therapy. (Hollander, J. L.: *J.A.M.A.* 172:306 [Jan. 23] 1960.)

SPECIAL PROBLEM: HYPERTENSION

Triamcinolone may be included among the currently available antirheumatic steroids having the least tendency to cause sodium retention. (Ward, L. E.: *J.A.M.A.* 170:1318 [July 11] 1959.)

Hypertension did not result from triamcinolone therapy. Existing hypertension was reduced sometimes. This may have been due to lack of sodium retention. (Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 [June] 1958.)

Precautions: Collateral hormonal effects generally associated with corticosteroids may be induced. These include Cushingoid manifestations and muscle weakness. However, sodium and potassium retention, edema, weight gain, psychic aberration and hypertension are exceedingly rare. In the treatment of rheumatoid arthritis, dosage should be individualized and kept at the lowest level needed to control symptoms. Dosage should not exceed 36 mg. daily without potassium supplementation. Drug should not be withdrawn abruptly. Contraindicated in herpes simplex and chicken pox.

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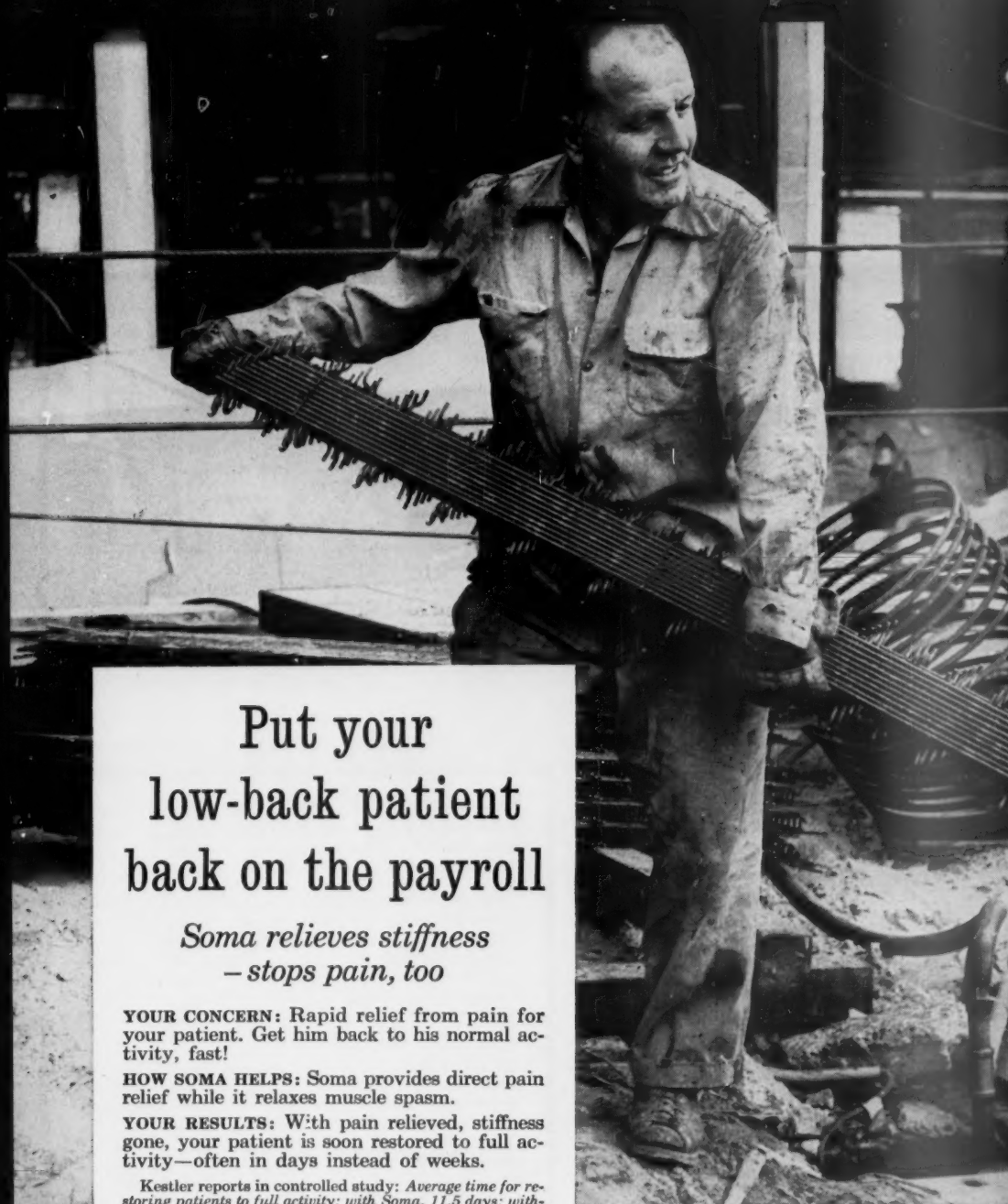
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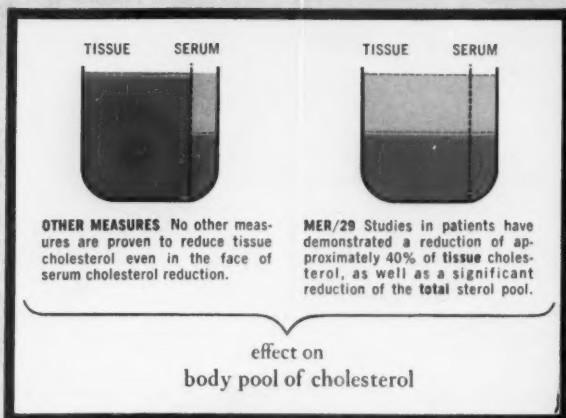
We know that MER/29 does this by inhibiting the body's own production of cholesterol.

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THE PROVEN AND PREDICTABLE BENEFITS OF MER/29

We know that, in some patients, concurrent clinical benefits attend the use of MER/29. Published papers on MER/29 therapy to date report improvement in 50 of the 79 anginal patients reported in these studies, and comparable results are being obtained in similar studies now in progress. Among the other benefits reported are:

- decreased incidence and severity of anginal attacks
- improved ECG patterns
- diminished nitroglycerin dependence
- increased sense of well-being



"During triparanol [MER/29] therapy there was a definite improvement in the electrocardiographic tracings in response to exercise in 3 of 11 subjects with angina pectoris."
—Hollander, W., et al.: *J.A.M.A.* 174:5 (Sept. 3) 1960.

"Nitroglycerin requirements decreased in 3 [of 5 out-patient] patients, including the patient showing electrocardiographic improvement....Three [of 4 private male patients], after a lapse of some weeks, showed improvement in exercise electrocardiograms, which was sustained but not further improved in subsequent observations."
—Corcoran, A. C., et al.: *Progr. Cardiovasc. Dis.* 2:(Pt. 1) 576 (May) 1960.

"Of the 45 patients with coronary artery disease followed for 1 year, 16 had a history of frequent anginal attacks. Fourteen of these spontaneously stated that their angina disappeared within 2 months of [MER/29] therapy....In one patient...with persistent coronary insufficiency pattern (ST segment depressions in multiple leads), there was a complete reversion to a normal tracing during MER/29 therapy with associated clinical improvement in angina."
—Lisan, P.: *Progr. Cardiovasc. Dis.* 2:(Pt. 1) 618 (May) 1960.

....what we are learning about atherosclerosis

WHY MER/29 MAY "DELAY" OR ALTER ATHEROSCLEROSIS

"It has become generally accepted that elevated blood cholesterol or lipid, if sustained long enough, leads to early atherosclerosis."

—Page, I. H.: *Mod. Med.* 29:71 (Mar. 20) 1961.

Epidemiologic studies show that low cholesterol levels are associated with low incidence of atherosclerosis and coronary artery disease.

On the basis of such studies, Stamler has said: "...a 15 to 20 per cent reduction in mean serum cholesterol levels alone might be associated with a 25 to 50 per cent reduction in coronary disease incidence rates in middle-aged men."

—Stamler, J.: *Am. J. Pub. Health* 50:(Pt. 2) 14 (Mar.) 1960.

THE DECISION FACING THE PHYSICIAN

Despite our knowledge of the action, benefits and safety of MER/29, much remains to be discovered about the basic concept of cholesterol-lowering therapy. In this, MER/29 is comparable to the well-accepted use of anti-hypertensive agents: we know they lower blood pressure, but we cannot prove that lowering blood pressure will also lower morbidity or mortality. Yet few physicians hesitate to use these agents. The possible good is too great to ignore.

So it is with MER/29. No one can yet be certain that sustained lowering of total body sterols

will prevent or alter atherosclerosis. But the current evidence strongly supports this concept.

Perhaps that is why an increasing number of physicians are now prescribing MER/29. They wish to assure their hypercholesterolemic, coronary artery disease, and atherosclerotic patients this reasonable hope.

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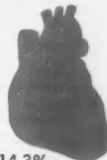
CHOLESTEROL: normal	CHOLESTEROL: above 260 mg. %	ELEVATED CHOLESTEROL: obesity hypertension
------------------------	---------------------------------	---



1.7%



8.0%



14.3%

—Adapted from Katz, L. N., and Pick, R.: *Heart Bull.* 8:82 (Sept.-Oct.) 1959.

MER/29

(triparanol)



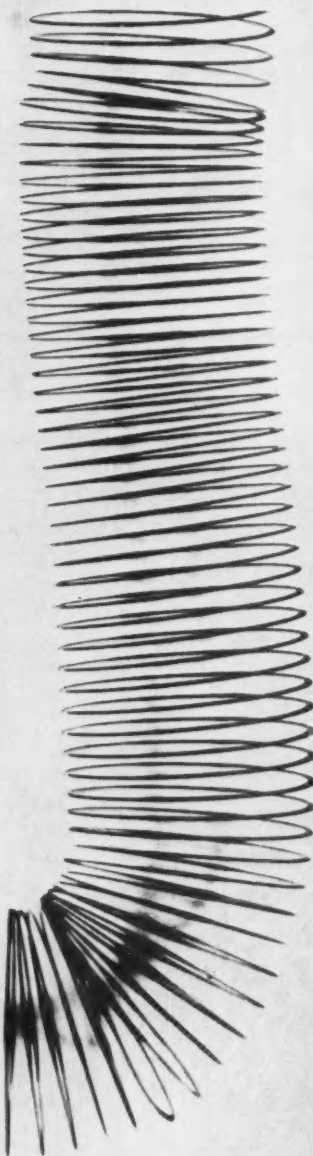
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*Nagy El Mahallawy, M., and Sabour, M. S.: J.A.M.A. 173:1783 (Aug. 20) 1960.

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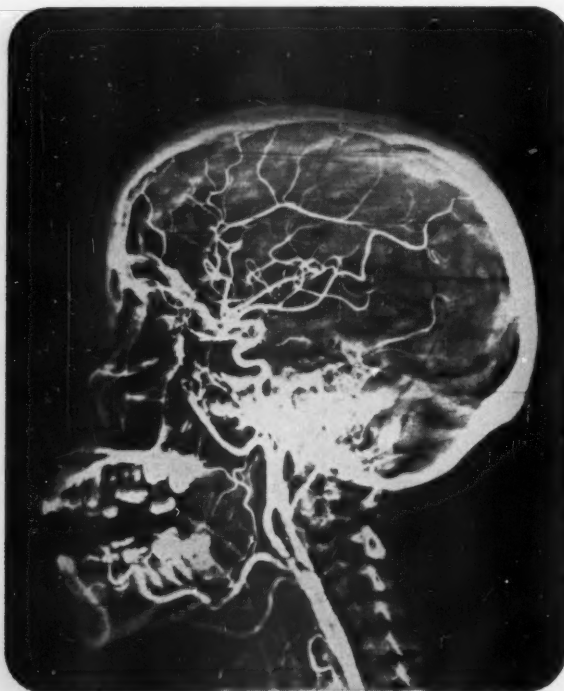
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References: (1) Doehner, G. A., and Brugger, G. E.: *New York State J. Med.* 60:4022 (Dec. 15) 1960. (2) Gensini, G. G., and Ecker, A.: *Radiology* 75:885 (Dec.) 1960. (3) Balkissoon, B.; Johnson, J. B.; Barber, J. B.; and Greene, C. S.: *J.A.M.A.* 169:676 (Feb. 14) 1959. (4) Agnew, C. H., and Cooley, R. N.: *Texas State J. Med.* 55:945 (Dec.) 1959. (5) Greenspan, R. H.; Bernstein, E. F.; and Loken, M. K.: *Am. J. Roentgenol.* 83:1034 (June) 1960. (6) Kruse, C. A.: *Western J. Surg.* 67:311 (Nov.-Dec.) 1959. (7) Barnett, J. C., and Arcomano, J. P.: *Radiology* 73:245 (Aug.) 1959. (8) Uts, D. C., and Thompson, G. J.: *Proc. Staff Meet. Mayo Clin.* 33:75 (Feb. 19) 1958. (9) Orr, L. M.; Campbell, J. L.; and Thomley, M. W.: *J.A.M.A.* 169:1156 (March 14) 1959. (10) Mathews, P. W. Jr.: *South. M. J.* 52:170 (Feb.) 1959.

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ANNALS OF INTERNAL MEDICINE

Volume 55

July 1961

Number 1

Essential Hypertension

Incidence, Course, and Heredity

SIR ROBERT PLATT, M.D., P.R.C.P., F.A.C.P. (HON.)

Manchester, England

FIRST OF ALL I MUST THANK YOU for the great honor you have done me in inviting me to come to your country and to give this lecture.

Much has been learned in recent years of the various causes of high blood pressure: coarctation of the aorta, pyelonephritis, aldosteronism, and renal artery stenosis. These are only some of the causes of what we call secondary hypertension. But whatever we do to refine our methods of diagnosis and investigation, we still find ourselves left with a group of patients with so-called essential hypertension of which we do not yet understand the cause. Moreover this group contains the great majority of patients who suffer from the effects of raised blood pressure. To some, essential hypertension is a diagnosis of exclusion, a mere category of discards into which we can throw any cases which cannot conven-

iently be diagnosed as something else. What I want above all to show you today is that essential hypertension is a specific disorder of blood pressure characterized particularly by its age incidence and its hereditary nature. Especially I want to convince you that essential hypertension is a hereditary disease in the same sense that Huntington's chorea is a hereditary disease, even though it be more influenced by environment and the nature of its inheritance be more complex.

In all that has happened in the field of hypertension in my time three concepts have particularly illuminated my thinking, and to two of these I modestly confess to having made a contribution. In 1947 I pointed out the frequency with which a family history of high blood pressure can be found in cases of essential hypertension (1). This of course had been realized before, but I think I was the first to suggest that it was sufficiently striking to be used as an aid to the diagnosis between essential and secondary hypertension. Secondly, in 1948 I showed that when severe hypertension occurred in younger persons under the age of 40, and especially under the age

Received for publication May 4, 1961.

Lilly Lecture presented at the Forty-second Annual Session of The American College of Physicians, May 8-12, 1961, Bal Harbour, Florida.

Requests for reprints should be addressed to Sir Robert Platt, M.D., P.R.C.P., Department of Medicine, Royal Infirmary, Manchester 13, England.

of 35, it was nearly always secondary and a cause for it should be sought and, if possible, found (2). What I did not realize at the time (for I was not then thinking as much in Darwinian terms as I do today), was that these two observations were closely connected. A hereditary disease that is as common as essential hypertension and as important a cause of death can occur only in the postreproductive years; otherwise it would be eliminated from the population by natural selection, although perhaps we must remind ourselves that it is only in the last few generations that constitutional hereditary conditions like essential hypertension have become important as a cause of death. Until a hundred years ago it mattered much more that you should resist the plague, the smallpox, the cholera, or the famine, and although those who did might live as many years as they do today, they were few in number.

The third concept which has helped me is the concept of malignant hypertension put forward first by Wilson and Byrom (3) in 1941 and second by Byrom and Dodson (4) in 1948 in two classical papers. The former showed that in the rat, as in the human, hypertension can be caused by unilateral renal ischemia and that when this was done by clamping a renal artery, the opposite kidney showed all the changes known as nephrosclerosis, whereas the clamped kidney, protected as it was from the effects of the high blood pressure, escaped. The second paper, by Byrom and Dodson, showed that the mere injection of fluid at high pressure into the arterial system of the rat could produce arteriolar necroses. In common with others I had observed that malignant hypertension did not occur in man unless the diastolic pressure had reached a level of about 140 mm Hg; enlightened by these papers I have ever since regarded malignant hypertension as the natural consequence of a blood pressure which has risen so high that the vessels are no longer adequate to support it.

In the patient's clinical history it is a sudden and disastrous change in symptoms and prognosis, but in terms of pathogenesis it is only a milestone (though a very important one) in the course of a progressive disorder.

Both the corollaries of this way of thinking are well proved: first, that malignant hypertension may be the end stage of any kind of hypertension, whatever its initial cause; and secondly, that anything that brings down the blood pressure to levels which the arterioles are capable of withstanding will cure the specific lesions of malignant hypertension if they have not already advanced too far.

The concept of essential hypertension as a specific disorder with a well-defined heredity and age incidence has become obscured rather than clarified, to my mind, by the papers of Hamilton, Pickering, Roberts, and Sowry (5, 6), and by subsequent papers from this group. These authors came to the conclusion that because there was no dividing line at which one could say with certainty that blood pressure was normal or abnormal, and because distribution curves of blood pressure in the population did not show a clearly bimodal form, essential hypertension was no more than the tail end of the distribution curve of a graded character like height or intelligence. Its heredity therefore must be multifactorial. This is in some ways an attractive hypothesis if one accepts the premises; but in fact none of their distribution curves are normal, and they failed to examine their data in ways which could critically decide whether essential hypertension was, or was not, a specific disorder of a specific age group. By working from populations rather than from *propositi*, by treating all first degree relatives as if they were a homogeneous group, and by losing sight of what I believe to be the specific behavior of essential hypertension with age, they came to the conclusion (erroneous in my view) that

the hereditary factor was a relatively slight one and that environment was probably of greater importance. It is not my purpose to describe in detail what I believe to be some of the fallacies in their argument, as I have already done this elsewhere (7, 8). I prefer to attempt to make a positive contribution to the study of essential hypertension, and because I felt that new data were essential, I have in the last six months examined or caused to be examined the blood pressure of 147 siblings of 93 patients attending our special follow-up clinic. These are all cases sufficiently severe, in our opinion, to require treatment by the powerful hypotensive agents now in use.

So long as we have only the blood pressure to go on, there is bound to be a place where the normal meets the abnormal and no man can say exactly where that is; indeed, it is an ill-defined and overlapping kind of boundary. I wanted therefore to ensure two things in my series: firstly, that there should be no doubt that all my cases from which the family data started (in other words, my probands, in the language of genetics) really had high blood pressure in the pathological range; secondly, that all cases of secondary hypertension were excluded as far as I could do so. In other words, they had to be my own personally investigated series of cases. The data in Table 1 will show you just how pathological they are. Note that they are almost exactly divided between the two sexes and that their mean blood pressure before treatment was as high as 240/142 mm Hg. Many of them were in the malignant phase. Of the 93 patients, 18 were considered after investigation to have secondary hypertension and 75 to have essential hypertension. Of these 75, heredity was clearly a factor in 56 (or three-quarters) either by the premature death of one or both parents from some disorder of a hypertensive nature, or by actually finding diastolic pressures of 100 or more (usually 110 or more) in the siblings. In 17 others the evidence was incon-

TABLE 1. Case Material: Hypertensive Probands and Their Siblings

Probands:	93
(46 M, 47 F, all white, 7 Jewish)	
Mean blood pressure before treatment: 240/142 mm Hg	
Secondary cases (age range 17 to 51 years)	18
Essential hypertension (age range 32 to 61; mean, 50 years)	75
Hypertension in parent(s) or sib(s)	56 (75%)
Evidence inconclusive	17
Remainder	2
No sibs, or none yet examined	26
Probands with siblings	67
Siblings of These 67 Hypertensives:	
Sibs examined	147
Sibs not yet examined	25
Sibs dead	29

clusive. If a parent has died of pneumonia at the age of 45, or has been killed in one of the wars, and the patient has no siblings, it is impossible to get a family history either to support or to refute the concept of essential hypertension as a hereditary disorder. In only two of the 75 cases was the evidence against hereditary factors in the sense that both parents had lived to an advanced age and two or more siblings had failed to show pathological blood pressures. Of course these two cases may have had secondary hypertension, the cause of which had not been revealed by our screening tests.

This is surely sufficient evidence by itself to convince you of the importance of heredity in essential hypertension; but before we go further into this fascinating subject let us first consider the behavior of persons with essential hypertension as we follow them through the middle years into the sixties. The question to ask is whether blood pressure rises with age in the whole population, or whether people with es-

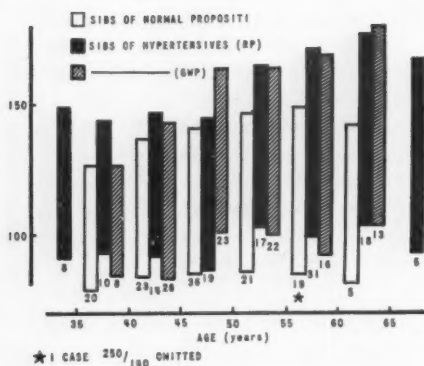


FIGURE 1. Blood pressure of siblings of normal propiati and of siblings of hypertensives (Platt and Pickering series) in age groups. The number of cases is shown beneath each column.

sential hypertension form a separate and specific group in which the blood pressure rises steeply to pathological levels. There is not much direct evidence on this question and what is really required is that the younger siblings of hypertensives be followed for 15 to 20 years. The studies of Thomson (9), of Cruz-Coke (10), and of Perera (11) on fairly large populations followed for years all seem to show that they do divide into two classes: those whose pressures rise but little with age, and those whose pressures rise steeply. These studies also show that the critical age is in the late forties or in the early fifties, though that is not to say that some do not rise before the age of 40. I do not wish to deal with these data at length, interesting and important though they are, because I particularly want to present the work which I have been doing myself expressly for this lecture.

Indirect but important evidence on the question of the behavior of blood pressure with age can be gained by comparing the siblings of patients with essential hypertension with the siblings of control cases without hypertension. You will see from Figure 1 that they behave quite differently. The siblings of the hypertensives have

slightly higher blood pressures even between the ages of 35 and 45, and this is because a few of them have already developed hypertensive levels; but there is no great rise until the 45-year age group in the Pickering cases and the 50-year age group in mine. Then the average pressures for the siblings of hypertensives rise to about 175/102 mm Hg by the age of 60 while the sibs of normotensives remain at about 145/85 mm Hg, a level close to the average for the general population in middle age. But please note that these pressures are averages and the real difference between the hypertensives and the controls is much greater than it appears if, as I hope to show you, the siblings themselves are of two kinds, those who have inherited hypertension and those who have not. The conclusions to be drawn from this part of the study are two: that essential hypertension seems to be a heritable disorder and those who inherit it behave in a different way from those who do not; and that if we are going to study essential hypertension it is necessary to study people at the age of 50 to 60 or, at the widest, 45 to 65. This is really a rather elaborate way of demonstrating what every clinician already knows from experience, that essential hypertension is a disorder of middle age.

If you agree that we must keep to a certain age group, then we must obviously study siblings rather than parent-child relationships. The parents of hypertensives are usually dead and the children are not old enough to show whether or not they are going to develop this hereditary disorder. Nevertheless, a retrospective parental history is interesting and valuable, as I have already shown you.

The key to the understanding of a phenomenon often comes from the observation of rather extreme examples. Figure 2 shows two sibships in which the brothers and sisters concerned quite clearly segregate into two types, the hypertensives and the normals. One example is from my own

data, and I could show you several more, and one is from Pickering's cases in which even the diastolic pressures of the two hypertensive sibs are higher than the systolic pressures of the two normals. Now this seems to me to be a case where it would be inappropriate and misleading to express the blood pressure of the siblings as an average of the whole. In the first family, if we average the blood pressures of the siblings of the *proposita*, we come to a figure of 170/102 mm Hg, which I have shown you is just about the mean for the siblings of hypertensives of that age. But if we use this average, we should completely lose sight of the fact that the sibs in this family are clearly of two distinct kinds; hence our study must be based not on averages but on distribution curves.

In 1959 I showed that if you applied these criteria to the data of the Pickering group (which the authors had failed to do), in other words, if you looked at distribution curves of blood pressure of siblings, aged 45 to 60, of their hypertensive cases, they arranged themselves in a curve which was very far from a normal distribution. I thought it was a bimodal curve but as I look at all these curves today I find that I had rather ignored a little lump in the

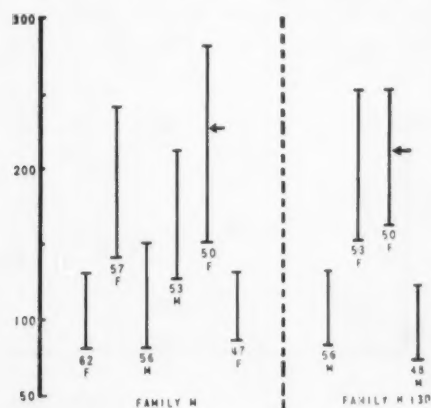


FIGURE 2. Distribution of blood pressure among siblings in two families.

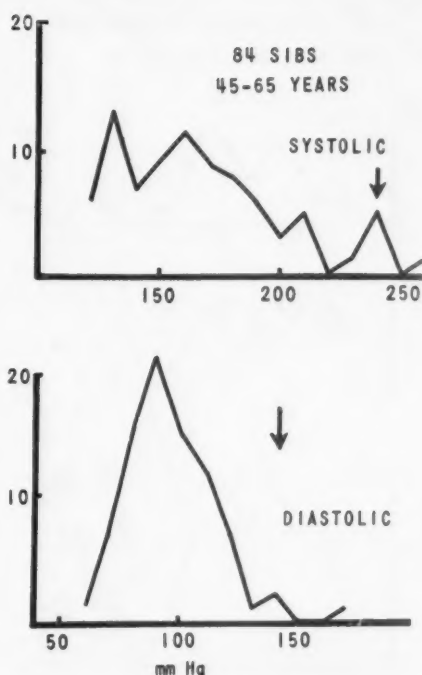


FIGURE 3. Frequency distribution curve of blood pressure of siblings of severe hypertensives. The arrows show the mean blood pressure of the *propositi*.

high range of the curve which I now think probably is important. Having collected my own data, I first looked at the 84 siblings aged 45 to 65 of my patients with severe essential hypertension. These are shown in Figure 3. The numbers are rather small, of course, because of the restricted age group we are studying, but by no stretch of the imagination could the systolic pressure curve be considered to be a normal Gaussian curve. The chart for diastolic pressure shows a bulge in the upper range and a small peak at the high pressure level. The arrows represent the mean pressure of the *propositi*.

In Figure 4 the data for systolic pressure in siblings of hypertensives in Pickering's series are added to my own, this time taking only siblings of *propositi* whose dias-

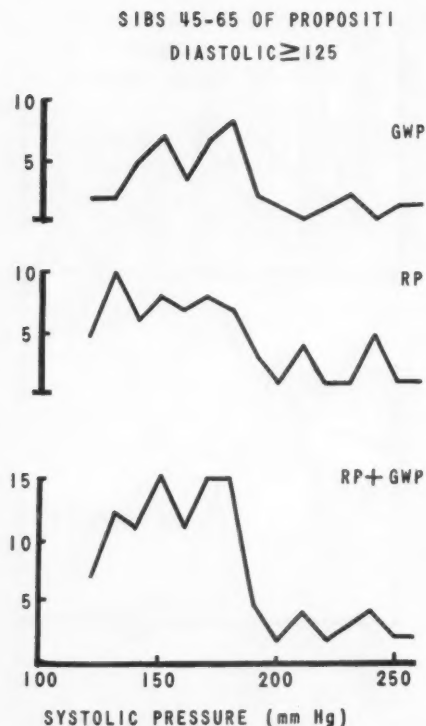


FIGURE 4. Distribution curve of systolic blood pressure of siblings of severe hypertensives (Pickering and Platt series).

tolic pressures were 125 or over. It may be that these curves are bimodal with a peak in the normal range and another in the 170 to 180 range, but there is again a third small hump in the high pressure region. I am not alone in thinking that blood pressure should perhaps be expressed logarithmically (12), and so I tried a logarithmic arrangement of my own data (Figure 5); it does look rather more as if there are three real peaks, though all the way through one wishes that one had more cases.* Once again we can be quite certain

* Because the blood pressures have been taken only to the nearest 5 mm Hg, the curve is plotted on the assumption that cases with blood pressures in the range of 120 to 129 are composed of equal numbers of cases whose pressures are 120, 121, 122, etc. This assumption does not have to be made for mean pressures as shown in Figure 6.

that these are not curves of normal Gaussian distribution such as we should be seeing if high blood pressure were simply a graded characteristic with a multifactorial inheritance.

I then hit on the idea of expressing mean pressures in logarithmic form, thus including both the systolic and the diastolic data in one chart. I took the mean pressure to be the diastolic pressure plus one-third of the pulse pressure (13). Figure 6 shows my own data and the Pickering data for siblings of hypertensives aged 45 to 65 treated in this way. Again you see a curve with three peaks, a curve which is certainly not a multifactorial Gaussian curve, because it is the wrong shape and there are too many normals. Before we try to interpret it, let us contrast it with the distribution curve of the siblings of normotensive controls from Pickering's data, which I show you in Figure 7. Here, as we would expect, we have a curve much nearer to normal, though it still sticks out in an awkward way at the high levels, and though it still might represent three peaks, at any rate for systolic pressure. Of course we must remember that some of these normal propiosti will be the siblings of hypertensives. We can also look at the siblings of cases of secondary hypertension in my series who again show a much more normal distribution curve, as do the siblings of hypertensives aged 30 to 49 before

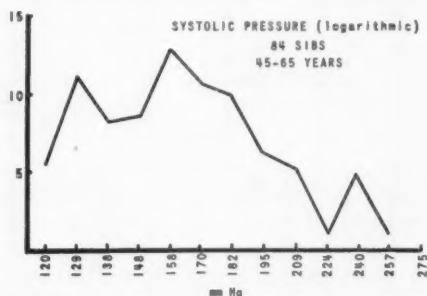


FIGURE 5. Distribution curve of systolic blood pressure of siblings of severe hypertensives (Platt series) logarithmically arranged.

most of them have developed hypertension (Figure 8). Here again we see a very normal distribution curve but with an added tail end in the hypertensive region. Let us come back to the curves with the three peaks in Figure 6, that is, the mean blood pressures of siblings logarithmically expressed in the Platt data and the Pickering data. I want now to be quite tentative and to speak only in terms of a hypothesis, which will need further evidence before it

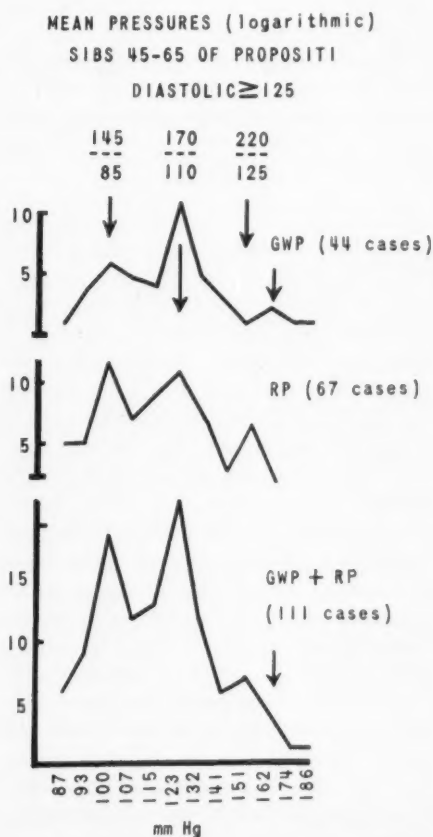


FIGURE 6. Distribution curve of mean blood pressure of siblings of severe hypertensives (Pickering and Platt series). The figures at the top give an indication of the mean pressure as it would be expressed in normal terms. The arrows on the extreme right show the mean pressure of the propositi.

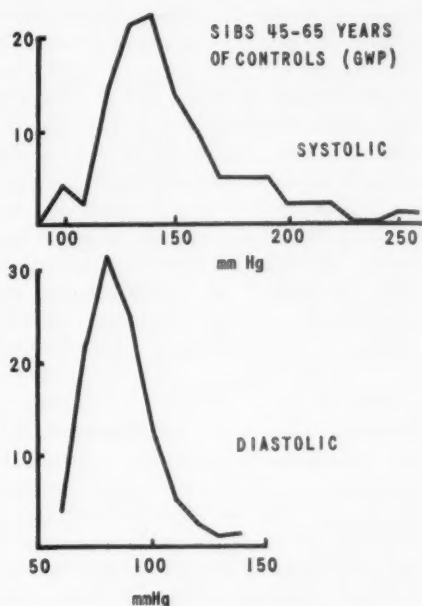


FIGURE 7. Distribution curve of blood pressure of siblings of normotensives (Pickering series).

is accepted or rejected. Is this possibly a real trimodal curve? Note first that the highest and broadest peak is intermediate between the high level of blood pressure of the propositi and the normals; from this we learn that the siblings of severe hypertensives may have normal, moderately high, or very high blood pressures, and that they seem to be sorting themselves out into these three groups. The majority are in the moderate range, which they would be if the multifactorial theory were right, but all the curves are of the wrong shape, as I have repeatedly shown. Is it possible that we are dealing with a gene or genes (experience has shown that in most common disorders more than one gene is concerned) of intermediate expression, that is, genes that are neither dominant nor recessive? If so there are in fact three phenotypes: the homozygote with two normal genes at one end of the curve, the homozygote with two abnormal genes at the other end of the

curve—the severe hypertensive who may develop malignant hypertension—and, in the middle, the heterozygote with the blood pressure in the 170/100 mm Hg range. Without going too deeply into genetics you may realize that if this is the case, and if the abnormal homozygote (the severe hypertensive) is less common than, say, 1 in 100 of the population, then the siblings of severe hypertensives should arrange themselves in a distribution approaching the 1:2:1 ratio, one normal, two heterozygotes with moderate hypertension, and one homozygote with severe hypertension. (The actual ratio would be nearer to 2:5:3 at this frequency, the normals always being fewer than the abnormal homozygotes.) We might then expect the distribution curve to look like a composite of the three triangles shown in Figure 9. If we turn again to Figure 6 we see that there are not enough cases at the severely hypertensive end of the curve to provide a reasonable approach to a 1:2:1 (or a 2:5:3) ratio, which you might think rather disappointing. But we have forgotten something. We have forgotten that there are still 25 siblings of these same cases in my series whom I have not yet been able to examine, and that there are 29 siblings who have died, not including those who died in childhood. I cannot speculate as to whether the siblings not examined and those who died of accidents, cancer, or

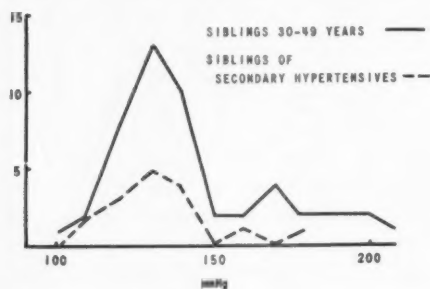


FIGURE 8. Distribution curves of systolic blood pressure in younger siblings of hypertensives and in siblings of secondary hypertensives (Platt series).

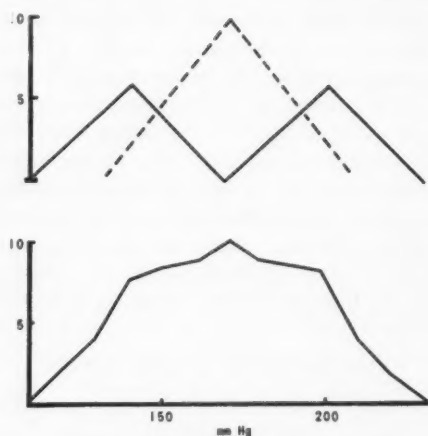


FIGURE 9. Showing how a composite curve would appear if composed of three populations overlapping with regard to their blood pressure.

pneumonia would or would not have been in the high blood pressure groups, but I know that nine of the siblings died of a stroke before the age of 55 or were known to have had high blood pressure, or both. If these nine siblings are distributed at the high end of my curve, it looks very much like the kind of curve we are expecting to see; but before we get too attached to the hypothesis I must remind you again that the numbers of cases are as yet insufficient for final conclusions to be drawn. Although I expect to publish a more extended series in due course, I hope that this preliminary communication will be of interest to you.

Having now, I trust, reinstated essential hypertension as a specific hereditary disorder, a conclusion strongly supported by the evidence of Morrison and Morris (14) and of Marshall (15), let me ask how common is it in the population? This I find impossible to answer in accurate terms, because the range of normal pressure no doubt overlaps with the low end of essential hypertension. What does seem to be clear is that in unselected population samples such as those of Miall and Oldham (16), and of Bøe, Humerfelt, and Weder-

wang (17) about 2% of the population at the ages of 45 to 60 have severe hypertension, that is, diastolic pressures of 120 and over, but this is reduced to 0.8% if we take diastolics of 125 and over.

My studies on heredity in hypertension have tended to confirm in my mind three things which may be no more than clinical impressions. The first is that I find it difficult to associate essential hypertension with any psychological or even any physical type in the population. It has been very interesting to meet the brothers and sisters of my hypertensive patients and to try to guess what their blood pressures may be before they are actually taken. I would have been wrong, I think, more often than right.

Secondly, I am inclined to agree with Cruz-Coke (18) and others that in cases classified as having pyelonephritic hypertension (though not in other secondary cases) the hereditary data are often equivalent to those found in essential hypertension. This may be simply because pyelonephritic episodes are common, and are not necessarily the cause of the hypertension, though I think that the evidence that pyelonephritis can be the sole cause of hypertension is very strong indeed.

Thirdly, I believe that pregnancy toxemia is rarely, if ever, the cause of permanent, severe hypertension. The question is a difficult one to investigate partly because of the difficulty of distinguishing between true pregnancy toxemia, the cause of which is still unknown, and pregnancy complicating essential hypertension. Examining the data of Gibson, I showed (19) that pregnancy toxemia seemed to be able to cause a slight and lasting elevation of blood pressure, but severe hypertension was so rare a sequel that the few cases might have been due to other causes. The series was based on a follow-up study which Gibson had done, in which 446 women were examined about four years after toxemic pregnancies in which the blood pressure

TABLE 2. Hypertension in Pregnancy

	Blood Pressure (mm Hg)
Mrs. C., born 1920:	
1st pregnancy ended December 1948	115/80 → 150/120
2nd pregnancy ended September 1950	150/100 → 130/90
3rd pregnancy ended November 1952	160/100 → 155/120
4th pregnancy ended January 1957	200/120
Seen May 2, 1957	200/130
ITSNBP* May 2, 1957	210/130

* See text.

had been taken and found to be normal during or before the twentieth week. Only three of these 446 women had a systolic blood pressure of 200 or over four years later.

Finally, before summing up, I wish to indicate how difficult it all is. Table 2 presents data from a woman who showed hypertension during four pregnancies; when I examined her four months after her last pregnancy, at the age of 37, her blood pressure was 200/130 mm Hg. But you will notice another blood pressure reading labeled ITSNBP which was taken on the same day and which is, if anything, a little higher. This case was published in 1958 (20). ITSNBP, I now reveal, means "identical twin sister, never been pregnant."

And now to sum up. I hope I have convincingly presented essential hypertension as a specific hereditary disorder. My main evidence for this is threefold. First, people with essential hypertension can be shown to have, with few exceptions, parents, siblings, or both, with the same disorder, if the data are available; of course in middle age parental data often are not available and few clinicians take the trouble to examine the blood pressures of the siblings. Second, in middle age the affected

siblings of hypertensives show a rise in blood pressure clearly distinguishable from the slight rise of pressure with age that takes place in the normal population. Third, whereas blood pressure in the general population shows a fairly normal (but never a completely normal) Gaussian distribution and is probably determined both by environmental and multifactorial hereditary factors, the distribution curves of blood pressure in the siblings of hypertensives are clearly incompatible with the notion that essential hypertension is only the extreme end of the normal curve. They indicate a different type of inheritance, perhaps giving rise to three forms of phenotype, the severely hypertensive, the moderately hypertensive, and the normal. We have as yet no final knowledge of the mechanism by which the high blood pressure is caused.

I have enjoyed doing the work for this lecture but hope you will regard my conclusions as tentative, awaiting a more thorough study of the heredity of essential hypertension which I hope some day to complete.

ACKNOWLEDGMENTS

My thanks are due to my secretary, Marion Winterbottom, who has done all the work of assembling 152 siblings (five have been added since the slides were made); to about 70 doctors in Britain, Belgium, and Australia who took blood pressures of siblings I could not reach myself; to The American College of Physicians for inviting me to give this lecture; and to the Eli Lilly Company for making it possible for me to do so.

SUMMARIO IN INTERLINGUA

Hypertension es presentate como un specific disordine hereditari. Le factos in supporto de iste assertion es le sequentes: (1) Il es possibile (si le datos es disponibile) demonstrar que subjectos con hypertension essential ha—con pauc exceptiones—parentes o frateros o parentes e frateros con le mesme disordine. (2) A medie etates le afficte frateros de hypertensivos monstra un augmento del tension de sanguine nettemente distinguibile ab le leve augmento

del tension de sanguine que occorre in le population normal con le avantiamento del etate. (3) Durante que le tension de sanguine in le population normal monstra un satis normal distribution gaussian e es probabilemente determinate per factores ambiental e per factores hereditari multifactorial, le curvas del distribution del tension de sanguine in le frateros de hypertensivos es clarmemente incompatible con le notion que hypertension essential es solmente le termino extreme del curva normal. Illos indica que differente typos de hereditate resulta in tres formas de phenotype: Le subjecto con hypertension sever, le subjecto qui es moderate-mente hypertensive, e le subjecto normal. Toxemia de pregnantia es raramente (si del toto) le causa de un persistente hypertension sever.

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Studies of the Pathogenesis of Human Hypertension

The Adrenal Cortex and Renal Pressor Mechanism

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AT THE MEETING of The American College of Physicians in Los Angeles in 1956 we reported our preliminary findings of a significantly greater urinary aldosterone excretion in patients with severe essential and malignant hypertension than in normal subjects. This study was based on a biological determination of a purified aldosterone fraction obtained after two successive chromatographic purifications of the crude, neutral extract of acidified urine (1). These studies of the relationship of adrenocortical hormones to hypertensive disease have been continued and, by using a more specific physicochemical method for the isolation and determination of urinary aldosterone, have been extended to a greater number of patients and to a wide spectrum of urinary corticosteroids. The relationship of aldosterone to the renal pressor mechanism has also been investigated.

Received for publication April 24, 1961.

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Presented at the Forty-second Annual Session of The American College of Physicians, May 8-12, 1961, Bal Harbour, Fla.

This work was supported by grants of the Ministries of Health (Federal-Provincial Plan), the Medical Research Council of Canada, the Life Insurance Medical Research Fund of New York, and the Ciba Pharmaceutical Co., Montréal.

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We will present first the results obtained in an extensive study of urinary aldosterone and pregnanetriol in normal subjects and in patients with various types of hypertension; second, the results of studies done during angiotensin infusions to normal subjects and to hypertensive patients in order to determine the effect on glomerular filtration rate, electrolytes, and aldosterone excretion; third, some preliminary data obtained with a new procedure for isolation and measurement of blood angiotensin in patients with arterial hypertension.

URINARY CORTICOSTEROID EXCRETION

SUBJECTS AND METHODS

The normal subjects were members of our laboratory personnel, who carried on their usual activities. The hypertensive patients were studied while in the hospital. None of the subjects were in congestive heart failure or presented any sign of edema. The normal subjects and hypertensive patients were on unrestricted diets, except for a few patients who were studied under metabolic balance conditions, with a fixed diet containing 102 and 90 mEq of sodium and potassium, respectively, per day. The criteria for classification of hypertensive patients and details of the various chemical and physicochemical procedures used for fractionation, purification, and determination of urinary steroids have been previously reported (2-4). The method used for urinary aldosterone was that of Nowaczynski, Koiw, and Genest (5). Two different procedures were used for preg-

TABLE 1. Urinary Corticosteroid Disturbances in Human Hypertension

		Hypertension		
	Normal Subjects	Essential	Renal	Malignant
<u>Aldosterone</u>				
No. of determinations	80	120	31	54
No. of patients	29	64	21	30
Mean & SE *	4.77 ± 0.37	12.2 ± 0.98	14.3 ± 2.52	16.9 ± 1.73
P		<0.001	<0.001	<0.001
<u>Pregnanetriol</u>				
A) Bongiovanni & Eberlein's Procedure:				
No. of determinations	11	33	9	15
No. of patients	10	26	8	12
Mean & SE *	2105 ± 271	991 ± 119	698 ± 150	770 ± 159
P		<0.001	<0.001	<0.001
B) Nowaczynski's Procedure:				
No. of determinations	22	46	8	23
Mean & SE *	954 ± 100	384 ± 53	342 ± 113	311 ± 64
P		<0.001	<0.005	<0.001
<u>Pregnanetriol/Aldosterone Ratio</u>				
A) Bongiovanni & Eberlein's Procedure:				
No. of determinations	11	31	8	12
Mean	358	104	104	51
			92% below normal range.	
B) Nowaczynski's Procedure:				
No. of determinations	10	45	7	21
Mean	133	30	22	19
			92% below normal range.	

* µg/day.

nanetriol determination, that of Bongiovanni and Eberlein (6) and that of Nowaczynski, Koiw, and Genest (7).

RESULTS (TABLE 1)

1. *Aldosterone:* Two hundred eighty-three determinations of urinary aldosterone were made in 142 normal subjects and hypertensive patients by our procedure. The groups of patients with essential, renal, and malignant hypertension show a three- to fourfold increase in mean urinary aldosterone excretion compared to that of normal subjects. Differences between means are statistically significant for the three groups ($P < 0.001$). Forty-three per cent of

all "spot" urinary aldosterone determinations in patients in the benign or severe phase of essential hypertension and in those in the malignant stage were above the upper limits of normal range (2 to 10 µg per day) by our procedure. Our findings of a mean increase in urinary aldosterone in patients with essential, renal, and malignant hypertension have been repeatedly confirmed (8-18).

Our results are derived from "spot" determinations in hypertensive patients. It is obvious that there is a marked overlapping in individual values obtained in normal subjects and hypertensive patients. For this reason, several normal subjects and patients

TABLE 2. Daily Urinary Aldosterone Excretion *

	Age	Dates	$\mu\text{g/day}$
Normal subjects			
R. D.†	30	Apr.; May (1960)	5; 6, 8, 7, 7, 5, 5, 3, 7, 3, 3, 3, 5, 4, 8, 6, 5
E. B.‡	27	Feb. (1958)	5, 2, 3, 5, 5
G. L.‡	25	June; Sept.; Nov. (1956)	2; 2; 4, 4, 6, 3, 2, 5, 2, 3
J. G.‡	36	June; July (1956); Feb. (1958)	7; 2; 2, 5, 4, 2, 8, 5
G. deL.§	22	Sept.; Oct.; Nov. (1956)	2; 8, 2; 3, 3, 3
Benign essential hypertension			
O. Ste M.‡	56	Nov. (1957)	10, 2, 2, 16, 15, 4, 9
P. R.‡	25	Jan.; Mar. (1959)	24, 24; 5, 4, 14, 14, 6, 5, 7, 9, 11, 20
U. P.‡	55	May (1957); June (1958)	7, 16, 4, 8, 14; 13
A. G.†	48	Jan. (1961)	11, 9, 21, 8, 8, 13, 15
L. deS.†	54	Jan. (1961)	16, 11, 26, 11, 18
Severe essential hypertension			
M. N.‡	42	Dec. (1958); Nov. (1959)	36, 5; 24, 7
Malignant hypertension			
F. R.‡	40	July; Aug.; Sept.; Nov. (1959)	37, 37; 20; 25; 27, 102
J. S.‡	45	July; Oct. (1959)	13; 32, 33, 44
J. M. D.‡	37	Dec. (1957)	26, 24, 4, 8, 9
F. L.‡	39	May (1959); Jan. (1960)	23; 29, 16, 26, 14, 20
L. L.‡	52	Mar. (1958)	1, 5, 3, 5, 3

* Procedure of Nowaczynski-Koiv-Genest.

† On fixed diet (102 and 90 mEq of Na and K per day, respectively).

‡ On self-selected diets.

§ On fixed diet of 150 mEq of Na per day.

Values in boldface type are abnormal. Values separated by commas are those for consecutive days, those separated by semicolons represent groupings according to corresponding months.

with various types of hypertension and at various stages of the disease were followed for daily determinations of their urinary aldosterone for periods of five to 20 consecutive days. Some were on a self-selected diet for the purpose of finding out what happens to urinary aldosterone under usual living conditions, while others were maintained on a fixed sodium and potassium intake, under metabolic balance conditions. As shown in Table 2, the daily urinary aldosterone excretion in normal subjects, whether on a self-selected or on a fixed diet, remained well within normal limits even when these subjects were carrying on their usual activities. This is especially striking inasmuch as variations in daily sodium intake of 50 to 390 mEq per day were noted in some subjects who were on self-selected diets.

On the other hand, all of the hypertensive patients studied, except for one patient with malignant hypertension who was followed for five days, showed excessive fluctuations of daily urinary aldosterone excretion ranging from normal to above normal levels. These fluctuations were more marked in subjects with severe and malignant forms of hypertensive disease, but they were also present in patients who were in the asymptomatic phase of benign essential hypertension. These slightly excessive fluctuations of urinary aldosterone in the benign hypertensive patients are in keeping with the mildly fluctuating blood pressure at this stage of the disease, and cannot be explained on the basis of edema (which was absent), nor on the basis of stresses, anxiety states, sodium restriction, or excessive potassium intake.

Venning et al. (8) have confirmed our findings of excessive daily fluctuations of urinary aldosterone in patients with primary benign hypertension, who were studied on a fixed sodium intake under metabolic balance conditions.

2. *Pregnane-3 α ,17 α ,20 α -triol*: Two series of normal subjects and of patients with essential, renal, and malignant hypertension were studied for excretion of pregnanetriol by different methods of analysis (Bongiovanni and Eberlein's [6] and Nowaczynski, Koiw and Genest's [7]). In both series, we found a highly significant decrease ($P < 0.001$) in mean pregnanetriol excretion in the groups of patients with essential, renal, and malignant hypertension, compared with that of normal subjects (Table 1).

3. *Urinary Pregnanetriol/Aldosterone Ratio*: Since the excretion of these two substances varies in opposite directions in hypertensive patients, their ratio may become a more sensitive index of the disease, in the absence of overt endocrine disorders. Results obtained by the simultaneous determination of urinary aldosterone and of pregnanetriol, as measured by either of the above mentioned methods, are shown in Table 1. In the two series of patients studied, this ratio was found to be below the lower limits of normal range in 92% of all hypertensive patients studied.

4. *Other Corticosteroids*: No significant difference was found in mean excretion of cortisol, cortisone, or their tetrahydro derivatives, in the excretion of etiocholanolone, and of the tetrahydro derivative of 17-hydroxy-11-desoxycorticosterone in groups of patients with essential, renal, and malignant hypertension compared to normal subjects.

ANGIOTENSIN INFUSIONS

As interesting as these findings on urinary aldosterone and pregnanetriol appear, it is quite impossible to overlook the role of the kidney in view of the clinical and experi-

mental evidence linking this organ to hypertensive cardiovascular disease. In addition, the experimental evidence of a close correlation between the granularity of the renal juxtaglomerular cells and the width of the adrenal zona glomerulosa (19) provided an added stimulant to our study on the relationship of aldosterone, sodium excretion, and the renal pressor mechanism.

Twelve normotensive medical students, two normotensive women with anxiety neurosis, and ten patients in the early benign phase of essential hypertension were studied. All subjects and patients were maintained on a fixed sodium and potassium intake (102 and 90 mEq/day, respectively) for periods of five to six days prior to and during the whole experimental period, under metabolic balance conditions.

The angiotensin used in these intravenous infusion experiments was the synthetic preparation of valine-5-angiotensin II, aspartic β -amide.* It is identical to that isolated from oxen by Elliott and Peart (20), except that the terminal aspartic acid was replaced by asparagine in the synthetic material. Acute (60 minutes) and long-term (three to 14 hours) intravenous infusions of angiotensin dissolved in 5% glucose were given. Studies were made on urinary volume, sodium and potassium excretion, glomerular filtration rate (as approximately measured by the endogenous creatinine clearance corrected to 1.73 square meters of body surface area), urinary aldosterone, cortisol and cortisone, and their tetrahydro metabolites.

RESULTS OBTAINED IN NORMAL SUBJECTS

Normal subjects respond to infusions of angiotensin which produce an average increase in diastolic pressure of 15 to 35 mm Hg above control levels with a significant decrease in sodium excretion and with a 10 to 40% fall in glomerular fil-

*Provided by Drs. Walter Murphy and Franz Gross, of the Ciba Pharmaceutical Company, Montreal and Basel.

TABLE 3A. Effects of Infusion * of Angiotensin on the Excretion of Sodium and Aldosterone
Normal Subjects †

Subject	J. M. (26, 2/14)‡		R. A. (22, 3.1/7)		R. A. (22, 3.4/13)		F. M. (31, 1.2/8)	
	Sodium§	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone
Day 1—Control	38	14	54	10	85	11	52	19
Day 2—Angiotensin, I.V.	14	52	22	14	31	105	38	32
—Postinfusion period	12	69	20	47	23	98	40	42
Day 3—Control	35	68	—	—	108	28	99	23
Subject	J. D. (21, 0.9/7)		H. N. (23, 0.9/12)		L. B. (24, 1.03/5)		A. L. (23, 1.09/5)	
	Sodium	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone
Day 1—Control	58	5	53	23	103	24	80	28
Day 2—Angiotensin, I.V.	6	36	16	84	7	107	13	120
—Postinfusion period	31	27	5	29	22	62	17	57
Day 3—Control	39	16	88	25	100	25	29	33
Subject	M. L. (24, 1.03/8)		R. L. (23, 0.85/8)		R. B. (22, 0.85/8)		G. P. (37, 0.525/5)	
	Sodium	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone
Day 1—Control	111	18	99	10	72	6	130	20
Day 2—Angiotensin, I.V.	63	90	35	95	15	44	57	138
—Postinfusion period	47	35	57	30	36	17	7	39
Day 3—Control	98	11	80	12	66	14	56	45

* Infusion of valine-5-angiotensin II, aspartic β -amide in amounts sufficient to produce an increase in diastolic pressure of 20 to 35 mm Hg above control levels.

† On a fixed intake of Na (102 mEq/day) and K (90 mEq/day) for five days prior to and during the experimental period.

‡ Numbers in parentheses indicate age in years and amounts (in mg) of angiotensin infused per number of hours.

§ Rate of sodium excreted: mEq per day.

|| Rate of aldosterone excreted: μ g per day.

tration rate (in most subjects). This fall in filtration rate is not constant since, in some subjects, a very marked sodium and potassium retention with lowering of the urinary Na/K ratio occurred without any change in creatinine clearance. These findings confirm on the whole those of Bock and Krecke (21) and of Peart and Brown (22, 23, 24).

As is shown in Table 3A, the long-term infusions of angiotensin given at a rate productive of hypertension were always accompanied by a two and one-half to 11-fold increase in urinary aldosterone excretion

and also by a concomitant rise in its reduced metabolite, pregnane-3 α ,18,21-triol-11,20-dione (also called tetrahydro-aldosterone) (25). This increase persisted in some subjects during the night period after the infusion and, in a few, even during the day following the infusion. This was always accompanied by a marked retention of sodium and a fall in urinary Na/K ratio. Changes in potassium excretion were slight in intensity and variable in trend.

An illustration of such studies in a normal subject (R. B.) is shown in Figure 1. This subject presented, during the angio-

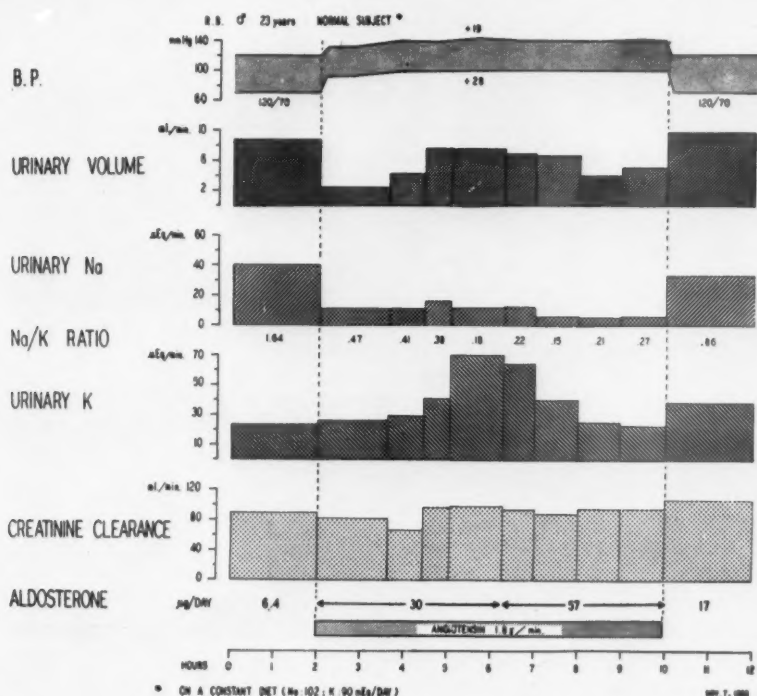


FIGURE 1. Effects of angiotensin infusion ($1.8 \mu\text{g}/\text{min}$ for 8 hr) given at a rate productive of hypertensive level to normal subject R. B.; note changes in urinary volume, sodium, Na/K ratio, potassium, creatinine clearance, and aldosterone. Stimulation of aldosterone is rapid, rising five to nine times its control value. This is accompanied by a marked decrease in urine volume, sodium excretion, and Na/K ratio. Potassium excretion rises to about three times its control value, then progressively returns to preinfusion levels. No significant effect on creatinine clearance (corrected to $1.73 \text{ m}^2 \text{ BSA}$, as in all other experiments) is noted.

tensin infusion, a significant decrease in urine volume, a constant and very marked sodium retention, and a fall in urinary Na/K ratio. Urinary potassium rose threefold before decreasing progressively to its control level at the end of the infusion. Creatinine clearance showed no significant change during the infusion, and urinary aldosterone rose from 6 to $30 \mu\text{g}$ per day during the first four hours and to $57 \mu\text{g}$ during the last four hours of infusion. Figure 2 shows the effects of a hypertensive infusion of angiotensin given to subject R. L. for eight hours, including a very marked sodium retention, a decrease in urinary Na/K ratio, and a greatly increased urinary

aldosterone excretion, which persisted during the night period following the infusion.

Subhypertensive infusions of angiotensin (i.e., given at a rate not sufficient to produce any significant rise in diastolic pressure) also increased urinary aldosterone two to three times that of control levels. They are usually accompanied by sodium retention. These effects are much less marked than those observed during angiotensin infusions given at hypertensive rates (26).

In order to determine whether the increase in urinary aldosterone was the result of the stress of the infusion experiments or the consequence of the artificially induced hypertensive state, 12 control infusions of

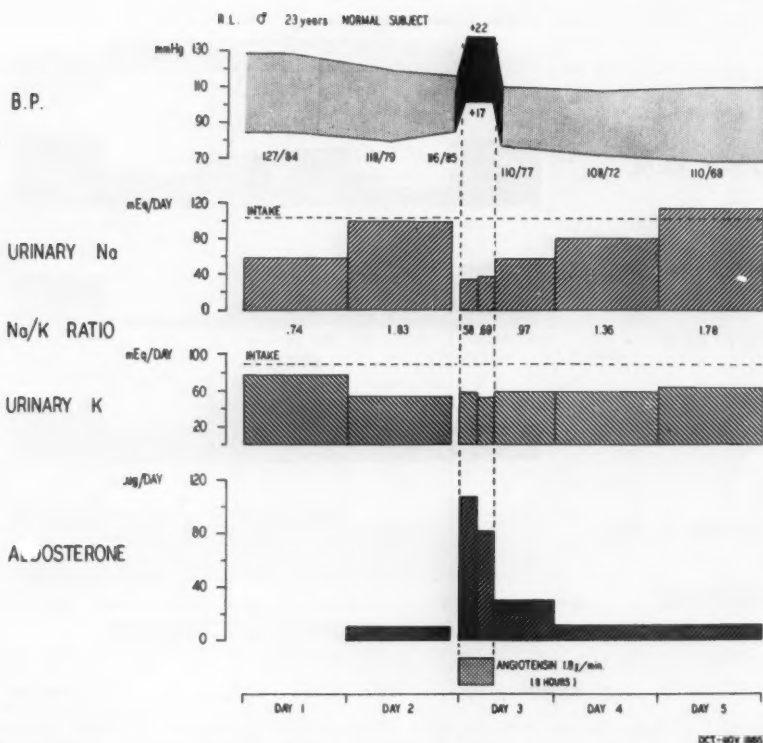


FIGURE 2. Effects of angiotensin infusion ($1.8 \mu\text{g}/\text{min}$ for 8 hr) given at a rate productive of hypertensive level to normal subject R. L., on urinary sodium, Na/K ratio, potassium, and aldosterone. Note the marked rise in urinary aldosterone and the simultaneous sodium retention during the infusion.

5% glucose in water, six infusions of epinephrine* and seven of norepinephrine† were given for periods of eight hours to nine normal subjects and four patients with essential hypertension. These infusions were without significant effects on urinary aldosterone (27), with two exceptions. In one instance, urinary aldosterone increased fivefold in a patient with benign essential hypertension during an infusion of 5% glucose and a twofold increase was noted during a norepinephrine infusion in a normal subject. Two phenylephrine infusions to two normal subjects were accom-

panied by a very pronounced natruresis and a twofold fall in urinary aldosterone (25).

RESULTS IN PATIENTS WITH BENIGN ESSENTIAL HYPERTENSION

All hypertensive patients responded to hypertensive infusions of angiotensin (with a further increase in diastolic pressure of 15 to 35 mm Hg above control levels) by a very marked natruresis and a simultaneous rise in urinary Na/K ratio (Tables 3B, 3C). As in normal subjects, urinary aldosterone excretion increased two to tenfold. This difference in sodium excretion in response to angiotensin between normal sub-

* Levophed, Winthrop Laboratories.

† Neo-synephrine, Winthrop Laboratories.

TABLE 3B. Effects of Infusion * of Angiotensin on the Excretion of Sodium and Aldosterone Patients with Benign Essential Hypertension †

Subject	M. H. (37, 0.445/8)‡		J. B. (52, 0.084/5)		H. D. (43, 0.180/2)		V. R. (43, 0.275/7)	
	Sodium§	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone
Day 1—Control	77	16	117	17	76	14	33	12
Day 2—Angiotensin, I.V.	255	69	318	54	137	70	39	58
—Postinfusion period	15	56	14	136	126	31	53	31
Day 3—Control	17	9	96	51	34	37	—	—

Subject	M. L. (42, 0.20/6)		M. L. (0.19/6)		J. R. (32, 0.300/6)	
	Sodium	Aldo-sterone	Sodium	Aldo-sterone	Sodium	Aldo-sterone
Day 1—Control	94	8	94	8	88	20
Day 2—Angiotensin, I.V.:						
(a)	431	44	146	46	268	114
(b)	—	—	—	—	308	51
—Postinfusion period	24	23	28	31	26	35
Day 3—Control	40	16	51	36	87	24

Footnotes (*, †, §, ||) are explained in legends for Table 3A.

TABLE 3C. Effects of Infusion * of Angiotensin on the Excretion of Sodium and Aldosterone Patient E.D.†† with Benign Essential Hypertension

	Sodium§	Aldosterone
Day 1—Control	77	5
Day 3—Control	42	12
Day 4—Angiotensin infusion, I.V. (0.200 mg/6 hr)	256	17
—Postinfusion period	32	10
Day 5—Control	19	8
Day 6—Control	56	15
Day 7—SU-4885, 4 g/day	91	7
Day 8—SU-4885, 4 g/day	90	
Day 9—SU-4885, 4 g/day	53	5
Day 10—SU-4885, 4 g/day; Angiotensin infusion (0.150 mg/6 hr)		
(a)	389	23
(b)	467	33
—Postinfusion period	41	7
Day 11—Control	39	10
Day 12—Control	52	14
Day 13—Control	28	10

Footnotes (*, †, §, ||) as in Table 3A.

†† Age, 52 years.

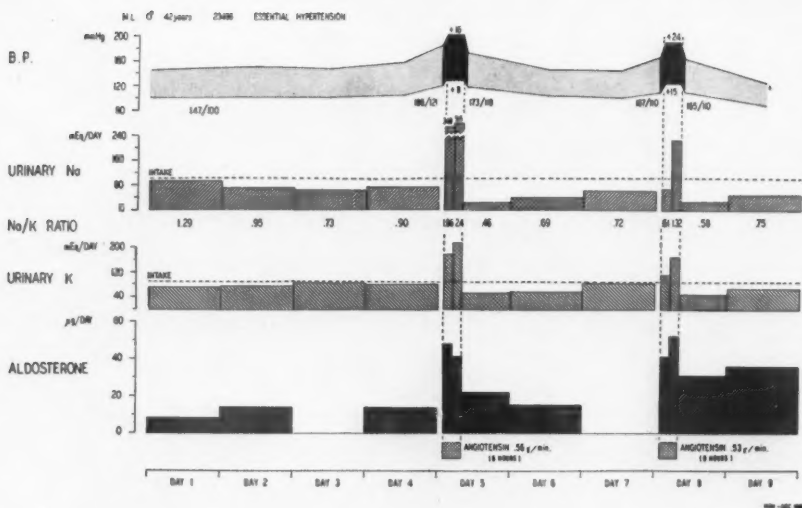


FIGURE 3. Effects of two angiotensin infusions ($0.56 \mu\text{g}/\text{min}$ for 6 hr and $0.53 \mu\text{g}/\text{min}$ for 6 hr) given at hypertensive rates (increase of 18 mm Hg and 16 mm Hg, respectively, in diastolic pressure above control levels) in patient M. L., with benign essential hypertension. Note changes in urinary sodium, Na/K ratio, potassium, and aldosterone. During both infusions, there was a marked increase in urinary aldosterone and kaliuresis. A profuse natruresis occurred during the first infusion and was much less marked during the second. In fact, no change in urinary sodium was noted during the first half of the second infusion. In this instance, the increase in urinary aldosterone persisted for at least 36 hr after the infusion.

jects and hypertensive patients, despite a similar rise in aldosterone, constitutes a fundamental problem to be solved.

A 43-year-old patient (M. L.) with benign essential hypertension received two angiotensin infusions given at hypertensive rates, three days apart (Figure 3). During the first infusion, there was a very marked natruresis, a less intense kaliuresis, and a rise in Na/K ratio, despite a threefold increase in urinary aldosterone. In contrast, the second angiotensin infusion produced a much more moderate natruresis, which appeared only during the last four hours of infusion, despite a similar increase in aldosterone excretion. Following this second infusion the urinary aldosterone persisted at an increased level for the next two days. The detailed studies done during these two infusions are shown in Figures 4 and 5. The difference in the intensity of the response in urinary sodium during these two infu-

sions raises the point whether the nervous stress which was more obvious during the first angiotensin infusion than in the second could have contributed significantly to the natruresis. It must be noted that the creatinine clearance increased 10% above control level during the first infusion.

Another type of study was done in a 52-year-old patient (E. D.) with benign essential hypertension who received two angiotensin infusions four days apart. The first infusion produced a marked natruresis despite a twofold increase in aldosterone excretion (Figure 6). The same patient was then given SU-4885* in a dosage of 750 mg every four hours. This substance is a potent inhibitor of the adrenal 11β -hydroxylase (28) and is therefore used for suppression of aldosterone and cortisol secretion. A sec-

* Metopiron provided through the courtesy of Drs. Walter Murphy and Carl Schaffenburg of the Ciba Pharmaceutical Company, Montreal.

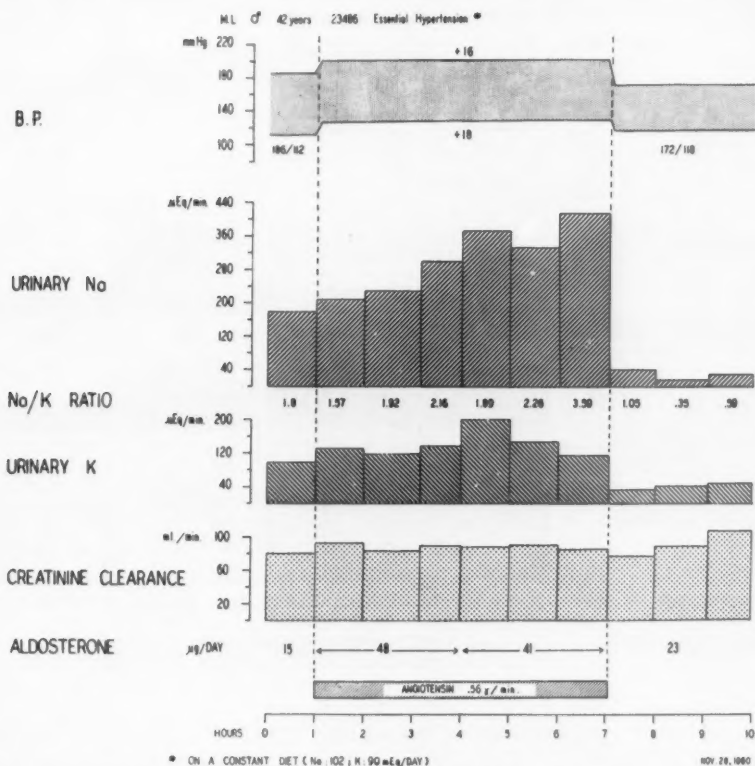


FIGURE 4. Effects of angiotensin infusion ($0.56 \mu\text{g}/\text{min}$ for 6 hr) given at a rate productive of a hypertensive level in patient M. L., with benign essential hypertension. Note changes in urinary sodium, Na/K ratio, potassium, creatinine clearance, and aldosterone. Note also the progressive and marked natruresis coinciding with a 10% rise in creatinine clearance (corrected to 1.73 m^2 BSA) and occurring despite a threefold increase in aldosterone. (Reproduced with permission from *Canad. Med. Ass. J.* 84: 403, 1961).

and angiotensin infusion done on the fourth day of administration of SU-4885 produced a more profuse natruresis. Despite the latter drug urinary aldosterone increased fourfold.

Subhypertensive infusions (without any significant change in diastolic pressure) of angiotensin to patients with benign essential hypertension produced a significant natruresis with a two to threefold increase in aldosterone excretion. These effects were less marked than those obtained during hypertensive infusions (26).

HUMAN BLOOD ANGIOTENSIN

These studies of the effects of angiotensin on aldosterone and sodium excretion in normal subjects and hypertensive patients appear of great interest from the pathogenetic point of view. But their importance and significance really depend on providing definite evidence for the existence of angiotensin in the blood of hypertensive patients. A highly sensitive and specific method has recently been described from our laboratory for the isolation of this polypeptide in a high degree of purity

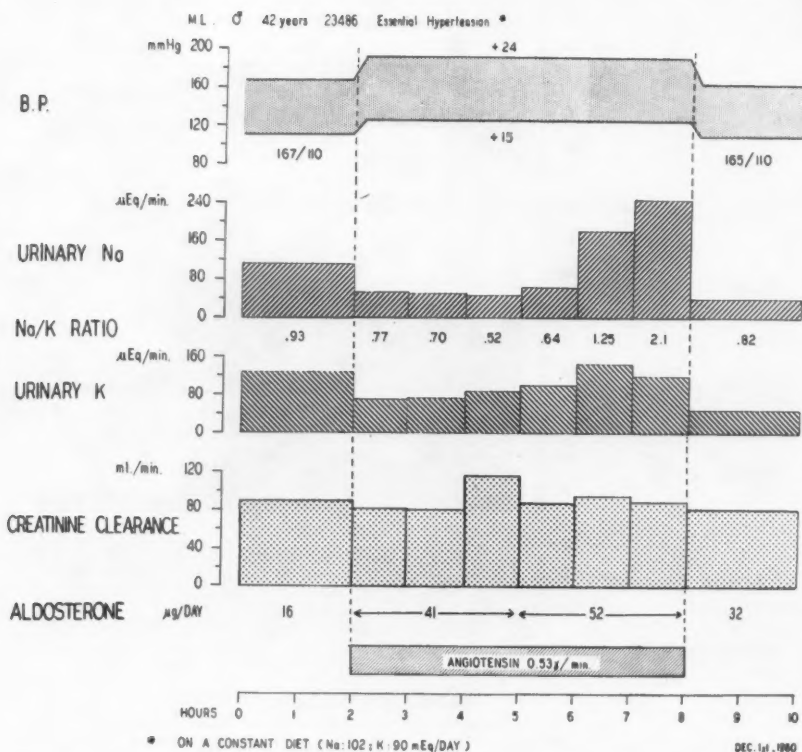


FIGURE 5. Effect of second angiotensin infusion ($0.53 \mu\text{g}/\text{min}$ for 6 hr) given at hypertensive rate, to the same patient as in Figures 3 and 4. Although the rate of angiotensin infusion and the further increase in diastolic pressure were the same as in the experiment illustrated in Figure 4, the natriuresis occurred only during the last two hours of infusion, without any significant change in creatinine clearance. Aldosterone stimulation was identical to that obtained during the first infusion.

from human blood (29). Although the description of the method is outside the terms of reference of this presentation, certain points can be emphasized: (1) The sensitivity is such that $5 \text{ m}\mu\text{g}$ of angiotensin give a rise of 15 to 20 mm Hg in the rat pressor assay used for quantitative determination of the isolated material; (2) The recovery of added angiotensin is quantitative; (3) The criteria of specificity, although indirect in nature because of the infinitesimal amounts making impossible a definite identification, are believed to be adequate (Table 4). Preliminary results

(30) in 60 normal subjects and hypertensive patients show that angiotensin is present in the blood of many hypertensive patients, and that there are also indications that it may participate in the homeostatic mechanism of blood pressure regulation. However, not enough data have been obtained to permit definite conclusions; these studies are still in progress. In order to determine the relationship of the angiotensin level in blood to the degree of rise in blood pressure, angiotensin was infused intravenously into seven normotensive medical students and their arterial or venous blood

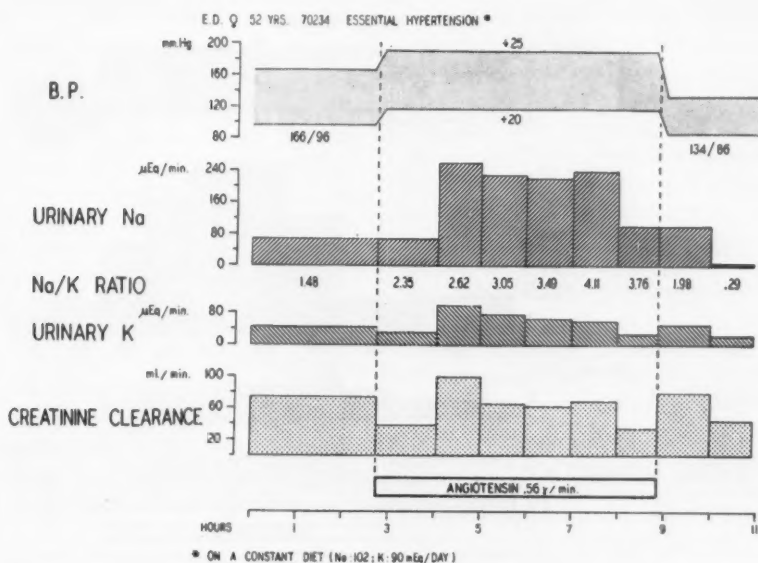


FIGURE 6. Effect of angiotensin infusion (0.56 μ g/min for 6 hr) given at hypertensive rate (with a further increase in diastolic pressure of 20 mm Hg above control level) in patient E. D., with benign essential hypertension. Note changes in urinary sodium, Na/K ratio, potassium, and creatinine clearance. There is a threefold increase in urinary sodium, and a rise in the potassium and Na/K ratio. Aldosterone excretion increased twofold during the infusion.

was analyzed for angiotensin levels. Results as given in Table 5 indicate that for a given degree of rise in blood pressure, the

angiotensin blood levels vary markedly from subject to subject, from 34 to over 200 μ g per 100 ml of blood.

TABLE 4. Similarities Between "Angiotensin" Isolated from Human Blood and Standard Valine-5-Angiotensin II, Aspartic β -Amide

- 1—Identical Rf values in paper chromatographic systems:
 - a) Sec. butanol: isopropanol:water:phosphate buffer pH 8 = 7:7:5:2 (Rf 0.55)
 - b) Butanol:acetic acid:water = 4:1:5 (Rf 0.35)
- 2—Identical migration in paper electrophoresis conditions: pH 6.2; ammonium acetate buffer; 5 volts/cm; 5 hr.
- 3—Identical pressor response curve in the rat bio-assay.
- 4—The angiotensin isolated from normal human serum following its incubation with a renin preparation (30) from renal tissue of a patient with unilateral renal hypertension * shows the same characteristics as the material isolated from hypertensive patients (see above: 1, 2, and 3).
- 5—Inactivated by trypsin.

Other Criteria:

Quantitative recovery of added angiotensin to blood with the same characteristics as mentioned in 1, 2, and 3. The angiotensin isolated from blood during infusion of this substance shows the same characteristics as the material isolated from hypertensive patients (see above: 1, 2, and 3).

* This patient had a complete occlusion of the right renal artery with a clinical and biochemical syndrome simulating primary aldosteronism.

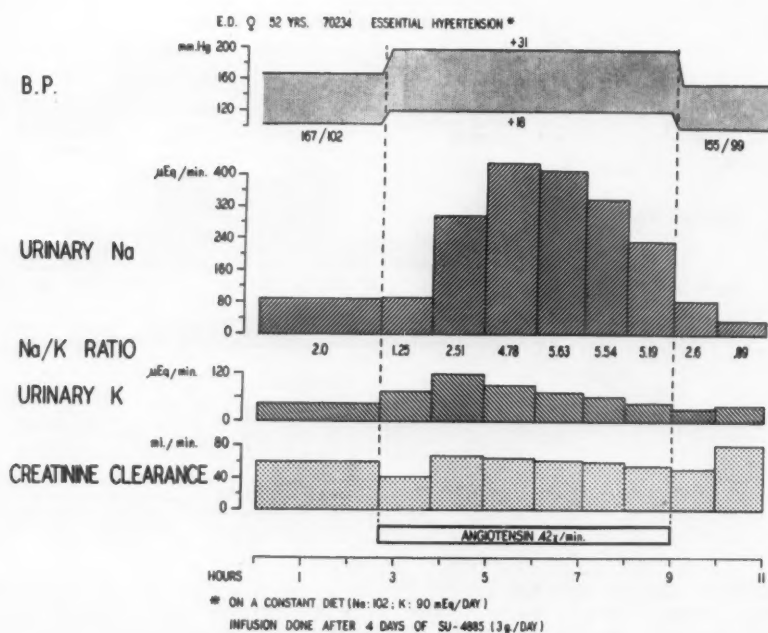


FIGURE 7. Same patient as in Figure 6, receiving an infusion of angiotensin ($0.42 \mu\text{g}/\text{min}$ for 6.5 hr) at hypertensive rate (with a similar increase in diastolic pressure as during the first experiment), on the fourth day of SU-4885 administration (750 mg orally every 4 hr). Note the very marked natriuresis and the rise in urinary potassium. Despite the administration of the 11β -hydroxylase inhibitor, aldosterone increased fourfold during the infusion.

TABLE 5. Effective Angiotensin Blood Levels * in Normal Subjects

Subjects	Rate of Administration ($\mu\text{g}/\text{min}$)	Average Increase in Diastolic Pressure (mm Hg)	Blood Levels ($\text{m}\mu\text{g}/100 \text{ ml blood}$)	
			Arterial	Venous
R. A.	6	30	200†	
J. P. B.	2.2	30	36	
J. P. B.	1.6	20		34
E. H.	2.5	31	114	
M. L.	1.9	36	130	
A. L.	3.8	30	34	14
M. M.	5.2	30	163 (1st blood sample†)	
			200 (2nd blood sample†)	
R. L.	2.9	30		33

* By constant intravenous infusions.

† 200 ml each.

DISCUSSION

Our findings of a mean increase in urinary aldosterone in patients with essential, renal, and malignant hypertension have been confirmed by Venning et al. (8) in an extensive study of 116 normal subjects and hypertensive patients. In Venning's study, all normal subjects and hypertensive patients were on a fixed sodium intake and under conditions of metabolic balance (aldosterone excretion in normotensive individuals on a sodium intake of 100 to 170 mEq per day was 2 to 12 μ g per day; mean: 5.1 ± 0.22), in contrast to our work where the great majority of subjects and patients were on self-selected diets. It is of interest that both of us have obtained almost exactly similar results. Venning et al. found that 75% of their normal subjects had urinary aldosterone values below 6 μ g per day, whereas 82% of their patients with essential hypertension excreted more than 6 μ g per day. In our study, exactly the same proportion (i.e., 75%) of normal subjects were shown to have urinary aldosterone excretion below 6 μ g per day, whereas 72% of patients with benign or severe essential and malignant hypertension have urinary aldosterone values above 6 μ g per day.

Laragh, Ulick, Januszewicz, Deming, Kelly, and Lieberman (31, 32) have studied the rate of daily secretion of aldosterone in patients with arterial hypertension. A normal secretion rate was found in patients with uncomplicated essential hypertension, whereas greatly increased rates were obtained in patients with severe essential and malignant hypertension.

Although the parameters measured by us and by Laragh et al. are somewhat different, the urinary findings in patients with benign essential hypertension are at variance with the normal aldosterone secretion rate obtained in similar patients by the latter workers, indicating probably a disturbance in metabolism and/or excretion of the hormone.

In addition, 55% of our patients with malignant hypertension had a normal urinary aldosterone excretion, contrasting with the extremely high aldosterone secretion rate obtained by Laragh et al. (31) in almost all their patients with malignant hypertension. In the group of patients with malignant hypertension studied by Laragh et al., 12 of 15 patients (80%) had a serum potassium below 3.8 mEq/liter, compared with a 40% incidence in our group of similar patients.

Since reporting our preliminary results of the specific and strong stimulation of aldosterone by angiotensin at the American Heart Association Meeting in Philadelphia in October, 1959 (33), cited by Tobian (19, 34), and at the International Symposium on Essential Hypertension in Bern in June, 1960 (35), our findings have been subsequently confirmed by Laragh, Angers, Kelly, and Lieberman (36), who have found an increase in aldosterone secretion in normal subjects who received angiotensin infusions.

The mechanism of action of angiotensin on sodium excretion may have at least three possible explanations: (1) The facts that the increase in urinary aldosterone is very rapid in some subjects, is present during infusions given at subhypertensive levels, and that sodium retention appears to be independent of any significant reduction in glomerular filtration rate in some subjects, support the concept that angiotensin exerts, in part, its effect on the tubular reabsorption of sodium through an increase in aldosterone secretion, as the present experiments and those of Laragh et al. (36) strongly indicate; (2) It is also possible that angiotensin acts directly on the renal tubules. Infusions given at hypertensive rates to two patients with proven Addison's disease who were receiving effective substitution therapy produced the same sodium retention and fall in urinary Na/K ratio as was observed in normal subjects. On the other hand, a patient who had a complete

bilateral adrenalectomy three years previously for primary aldosteronism, and who was maintained on substitution therapy, did not show any significant change in sodium and potassium excretion during a hypertensive infusion of angiotensin; (3) There is a strong possibility that in normal subjects who show a marked fall in glomerular filtration rate during angiotensin infusion, the decrease in sodium excretion may be due to reduction in the amount filtered by the glomeruli. The factors involved in the natriuresis shown by hypertensive patients in response to angiotensin infusion may be similar to those responsible for the increased tubular rejection of sodium of similar patients in response to salt loads (37).

The stimulatory effect of angiotensin on aldosterone is quite marked and specific. It is not the result of the induced hypertension per se, since it is also produced by infusions given at subhypertensive rates and is not encountered with similar hypertensive infusions of phenylephrine and norepinephrine (with one exception in seven experiments). Our findings seem to confirm the histological and experimental studies of Deane and Masson (38), those of Hartroft, Newmark, and Pitcock (39) and of Gross (40), which have demonstrated that renin administration produces a marked and rapid increase in the width of the adrenal zona glomerulosa in rats.

SUMMARY AND CONCLUSIONS

Our findings permit the following conclusions: (1) Definite abnormalities in urinary aldosterone, pregnanetriol, and pregnanetriol/aldosterone ratio have been demonstrated in patients with benign or severe essential hypertension and in patients with renal and malignant hypertension; (2) Angiotensin-II infusions stimulate specifically aldosterone both in normal and in hypertensive subjects; (3) Whereas this increased aldosterone during angiotensin infusions is accompanied by signifi-

cant sodium retention and lowering of the Na/K ratio in normal subjects, urinary sodium and the Na/K ratio increase markedly in patients with benign essential hypertension. This basic difference in response to angiotensin between normal subjects and hypertensive patients points to a fundamental problem which must be solved in order to obtain a better understanding of the disease; (4) Angiotensin has been demonstrated with an adequate degree of evidence in the blood of some hypertensive patients. These findings establish for the first time a direct relationship between the kidney and its renin pressor mechanism, the adrenal cortex, and sodium excretion in human hypertension.

ACKNOWLEDGMENTS

We wish to express our gratitude to Drs. Camille Dufault, Ihor Dyrda, Jean-Guy Hébert, and Gérard Tremblay, Medical Research Fellows; to Misses Fernande Salvail, Réjeanne Roy, and Pierrette Bourque, R.N.; to Mrs. Anne Brossard, dietician; and to Misses Pauline Robinson, Alice Laflamme, Isabelle Morin, Lucienne Monette, and Denise Landriault, medical technologists.

SUMMARY IN INTERLINGUA

Studios in nostre laboratorio ha establite definite anomalitates del activitate adreno-cortical in patientes hypertensive in comparison con subjectos normal. Tal anomalitates es:

1. Un significative ($P < 0,001$) augmento medie del aldosterona urinari in omne gruppas de patientes hypertensive (essential, renal, maligne).
2. Excessive fluctuationes diurne del aldosterona urinari in patientes con hypertension benigne e sever.
3. Un significative ($P < 0,001$) reduction medie del pregnanetriol urinari.
4. Un proportion pregnanetriol/aldosterona infra le limite inferior del region normal in 92% del patientes hypertensive.

Un relation directe inter le renes, le cortice adrenal, e natrium esseva demonstrate per le constatacion de un marcate e satis specific stimulation del aldosterona urinari durante e post le administration de valino-5-angiotensina II, aspartic β -amida per infusion intravenose a

rapidit tes hypertensive (i.e., con un augmento de 15 a 35 mm de Hg in le tension diastolic in supra del nivellos de control) in subjectos normal e in patientes hypertensive. Simile effectos, ben que minus marcate, esseva obtenite durante infusiones de angiotensina a rapidit tes sub-hypertensive (i.e., sin augmento significative in le tension diastolic). Le augmento del aldosteronuria esseva accompagnate de un marcate retention de natrium e un reduction del proportion de natrium a kalium urinari in subjectos normal, durante que patientes hypertensive respondeva per un profuse natriurese e un augmento del proportion de natrium a kalium. Secundamente, le relation directe inter le renes, le cortice adrenal, e natrium esseva etiam monstrate per le constatation del presentia de angiotensina in le sanguine de certe patientes hypertensive. Iste constatation esseva effectuate per medio de un nove technica pro le isolation e determination de angiotensina.

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The Effect of an Antithyroid Drug on the Clinical Course of Malignant Hypertension

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A NUMBER OF REPORTS HAVE BEEN MADE suggesting that antithyroid measures may suppress and that thyroid products may aggravate some of the effects of experimentally induced hypertension in animals (1-9). Some of these claim that the development or maintenance of an elevated blood pressure is modified, whereas others stress the influence of the thyroid on vascular pathology. It is accepted generally that surgical removal of the thyroid is without benefit in patients with primary hypertension, but at least one patient with advanced disease showed clinical improvement over a period of several months following thyroidectomy (10).

Inasmuch as the accelerated (malignant) form of hypertension is characterized by widespread arteriolar changes and presents many features which make it appear to be in a category separate from primary hypertension (11), the question was raised whether modification of thyroid function might exert an influence upon its course. This report presents four patients with malignant hypertension, whose disease did not seem to be related to a primary renal or endocrine disorder, and who were given methimazole in dosages sufficient to produce clinical or laboratory signs of hypothyroidism.

CLINICAL MATERIAL

All four patients, two men and two women, one of each being Negro, were between the ages of 36 and 42. None had a history, before therapy, suggestive of a primary renal disease. All had a family history of hypertension, at least a year of antecedent hypertension with repeatedly negative urinalyses, and then developed a clinical pattern characterized by proteinuria, diastolic blood pressures always 120 mm Hg or higher, and fundoscopic findings of hemorrhages, exudate, and papilledema.

Subsequent to the onset of this syndrome, all had elevated blood pressures in the legs, no stigmata of an endocrinopathy, and normal excretion of catechol amines; on intravenous pyelography they were found to have kidneys of normal size, shape, and position, which excreted dye in normal fashion. Impairment of renal function, as judged by the concentrating abilities of the kidneys or the excretion of phenolsulfonphthalein, was minimal in every instance. Blood urea nitrogen concentrations were less than 25 mg per 100 ml. None gave a history of a vascular accident, complained of cardiac pain, or had signs or symptoms of congestive failure; all had moderate cardiomegaly by X ray but no electrocardiographic evidence of myocardial damage.

Methimazole, 10 mg four times daily, was given to each patient beginning at least a month after the onset of the clinical picture of malignant hypertension. Two received no antihypertensive drugs before or during the study, while two were started on methimazole after receiving reserpine and

Received for publication April 12, 1961.

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Supported in part through the generosity of the Albert H. and Jessie D. Wiggin Foundation.

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hydralazine for three to four months. In these latter instances, the antihypertensive drugs were withdrawn gradually over a period of three months in one and 11 in the other; the methimazole was then continued alone.

All patients were ambulatory and were followed at intervals of three weeks or less, the blood pressure, retinal findings, and cardiac status being appraised on each clinic visit and a urinalysis being obtained. Complete blood counts, blood urea nitrogen and serum cholesterol concentrations, and basal metabolic rates or plasma bound iodine determinations were secured at regular intervals.

RESULTS

The two patients started immediately on methimazole had no fall or subsequent change in blood pressure, diastolic readings remaining 120 mm Hg or higher. Both gained weight, reported the disappearance of their moderately severe headaches, described themselves as being less nervous, and remained free of palpitation, dyspnea, edema, or cardiac pain. The mild nocturia of one patient continued. Within several weeks, the visual blurring of this patient had cleared; the other, initially unable to read even the headlines of a newspaper, was able to discern the fine print with clarity within two months. One or 2+ proteinuria persisted without change, and the blood urea nitrogen concentration stayed constant throughout the period of observation. Lethargy, dry skin, intolerance to cold, a rise in serum cholesterol, and a fall in the protein bound iodine to subnormal values appeared in both, but only after about three months of treatment, by which time all evidence of retinopathy had vanished in one patient, the other showing only residual macula "stars." One patient died abruptly after four months on methimazole alone of congestive failure following a presumed myocardial infarction; permission for an autopsy was not granted.

The other remains free of symptoms other than those of hypothyroidism, nine months after the start of treatment, still with marked hypertension, but with no retinopathy or progression of renal damage.

The two patients on antihypertensive drugs responded by minimal decreases in diastolic blood pressure to the 110 to 120 range, and by improvement in the retinopathy to the point of complete disappearance of hemorrhages, exudate, and papilledema. However, their blood pressures returned to the previous high levels after the addition of methimazole and the gradual withdrawal of the antihypertensive agents. Neither has complained of headache, visual symptoms, palpitation, nor has shown signs or symptoms of congestive failure since being on the antithyroid drug. Both slowly developed symptoms of hypothyroidism together with increases in serum cholesterol levels above 300 mg per 100 ml and protein bound iodine values of less than 3.6 μ g per 100 ml. There has been no return of retinopathy, no change in the degree of proteinuria, and no nitrogen retention for the period of observation, than those of hypothyroidism, nine months in one patient and for more than a year in the other.

The sequence of events in the patient followed for the longest period is noteworthy. After a year on methimazole alone he developed a mild pneumonia accompanied by a 24-hour period of fever, before responding to penicillin. His leukocyte response was adequate, and during and after this illness there was no increase or decrease in blood pressure. Inadvertently, he was given a cough medicine containing potassium iodide for a few days and, over the course of the next three weeks, he developed a large and minimally tender goiter. The methimazole was then discontinued for a three-week period and thyroid was administered in 30 mg doses daily. During this interval the blood pressure remained unchanged, he lost weight, and

the goiter diminished in size. The serum cholesterol fell from 353 to 195 mg per 100 ml, the blood urea nitrogen rose slightly from 23 to 27 mg per 100 ml, and, for the first time in more than a year, he complained of severe frontal and occipital headaches as well as visual blurring. Examination of the optic fundi disclosed a return of definite blurring of the disc margins but with no hemorrhages or exudate. After the three weeks on this regimen, thyroid administration was discontinued and methimazole was resumed in the previous dosage. During the ensuing month he gained weight, there was gradual disappearance of the headaches, and the disc margins became outlined clearly. Now, three years after the onset of the accelerated form of hypertension, more than two years after the start of methimazole, and 17 months without any antihypertensive drugs, his picture is as follows: blood pressure 210/150 mm Hg, no retinopathy or congestive failure, proteinuria 2+, blood urea nitrogen 24 mg per 100 ml, and he is asymptomatic save for mild signs and symptoms of hypothyroidism.

DISCUSSION

This preliminary clinical study, which suggests that an antithyroid drug may interfere with the progression of the accelerated form of hypertension, calls for several comments. First, the diagnosis was made on presumptive grounds and primary renal disease, unilateral or bilateral, cannot be excluded with certainty. However, the sequence of events, the antecedent hypertension without renal involvement, the minimal proteinuria in the face of marked hypertension, and the normal pyelography are strong support for the malignant label.

One might ask also whether the reversal of retinopathy and the course of these patients fit into the known variations in pattern which can occur in the evolution of this disease. Although retinopathy rarely

may improve or disappear spontaneously, and it is reported that an occasional patient survives for more than two years (12, 13), these are exceptional situations. In this clinic, none of 200 documented patients with malignant hypertension who received no antihypertensive measures failed to show progressive renal insufficiency with azotemia or lived longer than 22 months; the average survival was far less than one year. In another group treated with strong and effective antihypertensive drugs, their withdrawal because of reactions or other reasons resulted invariably in almost immediate exacerbation of the underlying disease.

It remains to be seen whether other antithyroid measures, such as thiouracil derivatives, radioactive iodine, or surgery, will modify the course of malignant hypertension or whether the action of methimazole, if confirmed, is a unique property of this drug. In two patients, note must be made of the fact that the improvement in retinopathy was associated with no antihypertensive drugs and no decrease in blood pressure, and began before clinical or laboratory evidence of hypothyroidism.

This study calls for confirmation and extension. Although it raises the possibility that methimazole or other antithyroid measures may have therapeutic implications in patients with the accelerated form of hypertension, it poses more the question of possible mechanisms. One wonders whether methimazole interferes with autonomic nervous system responses or whether a decrease in thyroid activity at a tissue level blocks the development or progression of necrotizing arteriolitis.

SUMMARY

Four patients with the accelerated (malignant) form of hypertension were treated with methimazole. Two received no antihypertensive drugs, while two were started on the methimazole while receiving anti-

hypertensive drugs which were subsequently withdrawn.

While these patients were on the antithyroid drug alone for periods of from four months to over a year they remained free of hypertensive symptoms, showed complete clearing or no recurrence of retinopathy, and developed no further renal dysfunction.

Improvement or the absence of progression occurred without a fall in blood pressure and began before clinical or laboratory evidence of hypothyroidism. Although this preliminary study may have therapeutic implications, it is presented in order to stimulate inquiry into possible mechanisms.

SUMMARIO IN INTERLINGUA

Quatro patientes con le forma accelerate (maligne) de hypertension esse tractate con methimazol. Duo recipeva nulle drogas anti-hypertensive, durante que le altere duo esseva initiate in le tractamento con methimazol a un tempore quando illes recipeva drogas anti-hypertensive, sed istos esseva discontinue sub-sequentemente.

Durante que illes recipeva solmente le droga antithyroide—durante periodos de inter quatro menses e plus que un anno—omne le quatro patientes esseva libere de symptommas de hypertension; illes monstrava un acclaration complete de retinopathia o nulle recurrentia de illo; e illes non disveloppava ulle nove dysfunction renal.

Melioration del morbo o interruption de su progresso occurreva sin declino in le tension del sanguine e comenciava ante le apparition de signos clinic o laboratorial de hypothyroidismo. Ben que iste studio preliminar es possiblemente de signification therapeutic, illo es publicate pro stimular investigationes del mecanismos subjacente.

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Factors of Risk in the Development of Coronary Heart Disease— Six-Year Follow-up Experience

The Framingham Study

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INCREASINGLY RELIABLE ESTIMATES of the prevalence and incidence of coronary heart disease (CHD) emphasize the importance of this disease as a contemporary health hazard. Cardiovascular disease is now the leading cause of death, with coronary heart disease accounting for two-thirds of all heart disease deaths. While advances in the diagnosis and therapeutic management of CHD have been made in the past decade, no important reduction in morbidity and mortality from CHD has occurred. This is apparent in the relatively slight increase in life expectancy at age 40 which has been achieved in the past several decades, while life expectancy at birth has been substantially prolonged.

Because coronary heart disease is often manifested as sudden unexpected death or "silent" infarction and since the immediate mortality in those surviving to enter a hospital is still distressingly high in spite of the best therapeutic efforts, it appears that a preventive program is clearly necessary.

Received for publication April 19, 1961.

From the Heart Disease Epidemiology Study, Framingham, Mass., and the National Heart Institute, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Washington, D. C.

Presented at the Forty-second Annual Session, The American College of Physicians, May 8-12, 1961, Bal Harbour, Fla.

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Since it has been established that coronary atherosclerosis is present for many years prior to the development of symptomatic CHD, it seems evident that efforts at prevention must begin many years before the appearance of clinical CHD. A knowledge of the epidemiology of the disease is highly desirable if a program of prevention is to be developed. From a study of the characteristics of persons who develop coronary heart disease under observation in comparison with those who remain free of disease it is possible to determine the characteristics of susceptible individuals. This allows the identification of the coronary prone individual many years before the occurrence of clinically recognizable disease.

Multiple interrelated factors have been demonstrated to be associated with increased risk of development of CHD. To date no single essential factor has been identified. However, epidemiologic information has accumulated which now allows the physician to recognize certain characteristics of increased risk in patients he sees in his practice. Some of these characteristics have been convincingly demonstrated, others are still under investigation. More precise identification will undoubtedly be possible in the future.

The present report deals with three characteristics believed to be associated with proneness to the development of CHD: elevated serum cholesterol levels, hypertension, and the electrocardiographic pat-

tern of left ventricular hypertrophy. These characteristics have been demonstrated to be associated qualitatively with the development of CHD in a previous report (1). No precise estimate of the magnitude of the increased risk could be made at that time. The present report represents two more years of observation and allows more detailed analysis of these factors as they affect both men and women. Sufficient data have now been accumulated to permit quantitative estimation of the increase in risk associated with these characteristics singly and in combination.

Because of the apparent need to obtain more epidemiologic data in coronary heart disease, a study was established in Framingham, Massachusetts, during the period 1948 to 1950. The Framingham Study was designed to investigate the incidence of cardiovascular disease and factors related to its development. Details of the organization and first four-year follow-up experience have been previously reported (1-5).

METHODS

A description of the town of Framingham, the method of selection of the study population, and the response of selected persons has been previously reported (1, 5, 6). Of the 6,507 persons selected at random, 4,469 persons aged 30 to 59 came in for examination and comprised the sample population. An additional 740 persons who volunteered to cooperate in the Study have also been included. The rationale for including the group of volunteers has been discussed elsewhere (1, 5). While the sample and volunteer groups differ in a number of minor particulars, none of the recorded differences appears to present any difficulties in analysis (5). The incidence of new coronary heart disease in the two groups is very similar. Accordingly, these two groups have been combined.

All subjects have been examined in a clinic set up for the Study. A detailed history and a physical examination were com-

pleted by a physician assigned to the Study and the findings were entered on standard forms. If any possibility of the new development of CHD was considered, the opinion of a second physician was obtained. Laboratory studies included chest X ray, electrocardiogram, vital capacity determination, urinalysis, hemoglobin, hematocrit, blood glucose, uric acid, lipoproteins, cholesterol, phospholipid, and other special studies.

Upon completion of each examination a diagnosis was made using uniformly applied criteria as indicated below. An abstract of the findings was sent to the personal physician indicated by the subject. No medical advice was provided to any participant beyond encouragement to visit his physician if the need was indicated.

CRITERIA FOR CORONARY HEART DISEASE

The criteria used for the classification of coronary heart disease in the Framingham Study are based upon those recommended by the New York Heart Association (7).

1. Angina pectoris: Minimal criteria for the diagnosis of angina pectoris consisted of substernal discomfort of brief duration (i.e., two to three minutes), definitely related to exertion or emotional upset, promptly relieved by rest, and seldom if ever occurring during periods of quiet or rest. The diagnosis was made when symptoms were sufficiently clear cut to allow at least two observers to agree readily as to its presence. Because of the subjective nature of this diagnosis, no possible or questionable instances are included in the group designated as having coronary heart disease.

2. Myocardial infarction: This diagnosis was made only in the presence of electrocardiographic changes of infarction.* All

* Recent or acute myocardial infarction was designated when S-T segment elevation was present associated with late inversion of T waves and the occurrence of loss of initial QRS potentials (i.e., development of "pathological" Q waves of four

TABLE 1. Composition of Framingham Study Group

	Total	Men	Women
Random sample	6,507	3,074	3,433
Respondents	4,469	2,024	2,445
Volunteers	740	312	428
Respondents free of CHD*	4,393	1,976	2,417
Volunteers free of CHD	734	307	427
Total free of CHD: Framingham Study Group	5,127	2,283	2,844

* Coronary heart disease.

hospital records and electrocardiograms were reviewed by the Study personnel. In cases that lacked a history, the development of an unequivocal pattern of myocardial infarction since the previous electrocardiographic tracing was obtained, was accepted as evidence of an unrecognized myocardial infarction. In addition, for the purpose of the present analysis, instances of prolonged acute coronary insufficiency with associated electrocardiographic abnormality were included in this category.

3. Sudden death: This was considered to be due to CHD when it was documented to have occurred in a matter of minutes and was attributed to no other cause by the physician who completed the death certificate and when no other cause of death was suggested by prior medical history. All death certificates and information

hundredths of a second duration or greater), followed by serial changes of evolution if available.

An old or remote myocardial infarction was considered to be present when there was a pathological Q wave of four hundredths of a second duration or greater, or loss of initial QRS potential (R-wave) in those leads in which this would not be expected to occur. This electrocardiographic diagnosis was also considered when changes from a previous tracing indicated a loss of R wave potential previously present and not otherwise explained. More weight was given to this finding if T wave abnormality was also associated. In all instances electrocardiograms antedating the event were available for comparison, a factor of considerable assistance in evaluating patterns of old myocardial infarction.

available regarding the death of the patient were reviewed by clinic personnel.

Whenever available, autopsy information was utilized only to confirm the clinical diagnosis of CHD. The autopsy rate was not high enough to use post-mortem findings as a basis for diagnosis.

COMPOSITION OF STUDY GROUP

Table 1 shows the composition of the population being observed for the development of coronary heart disease. The population at risk of developing CHD consisted of those persons who were free of this disease at the initial examination. Of the 6,507 persons selected for study, 4,469 responded and were examined. Of these, 4,393 were found to be free of CHD and were suitable for follow-up study. Of the 740 volunteers, 734 were free of disease. Thus, a group of 5,127 persons free of CHD on entry to the study could be periodically re-examined for the subsequent development of disease; they constituted the Framingham Study Group.

FOLLOW-UP

Of the original study group it was possible to re-examine 87% at the clinic on the fourth biennial examination or later (Table 2). Another 2.4% are known to have died before their fourth examination was due. For this group the cause of death has been ascertained and in each instance

TABLE 2. Six-Year Follow-Up: Framingham Study Group

	Number	Per Cent
Framingham Study Group	5,127	100.0
Examined at clinic at Exam IV*	4,478	87.3
Not examined at clinic at Exam IV*	649	12.7
Dead before Exam IV*	122	2.4
Alive at Exam IV*	523	10.2
Unknown whether alive or dead	4	0.1

* Fourth biennial examination.

TABLE 3A. Six-Year Incidence of CHD* by Age and Sex

Age at Entry	Framingham Study Group		Sample Respondents		Volunteers	
	New CHD	Population at Risk	New CHD	Population at Risk	New CHD	Population at Risk
Men	125	2,283	106	1,976	19	307
30-34	5	388	4	333	1	55
35-39	11	438	9	388	2	50
40-44	15	420	13	357	2	63
45-49	15	352	14	308	1	44
50-54	27	353	19	301	8	52
55-59	41	262	36	221	5	41
60-62	11	70	11	68	—	2
Women	61	2,844	52	2,417	9	427
30-34	—	453	—	388	—	65
35-39	—	582	—	489	—	93
40-44	3	508	3	433	—	75
45-49	16	446	13	376	3	70
50-54	14	421	10	357	4	64
55-59	24	371	22	313	2	58
60-62	4	63	4	61	—	2

* Coronary heart disease.

documentation has been sought to determine whether coronary heart disease had developed by the time of death. From observation of the population at subsequent examinations at the clinic, routine surveillance of admissions to the local hospitals, and inquiries made of friends and relatives appearing at the clinic for examination it was possible to reach a conclusion about the state of health with respect to CHD for another 10.2%. In many instances the physicians of the community, knowing of our interest in the problem, have advised us of the development of new disease in our subjects. It is considered to be unlikely that a significant number of new events of CHD have been missed in the six years of follow-up.

RESULTS

INCIDENCE AND CLINICAL MANIFESTATION OF HEART DISEASE IN SIX YEARS OF OBSERVATION

The incidence of coronary heart disease (defined above as myocardial infarction, angina pectoris, and sudden death) is shown in Tables 3 A and B. The population at risk

for this observation was composed of all subjects found to be free of CHD at entry into the Study. There were 186 men and women free of definite CHD at the first examination who developed the disease in the subsequent six years of observation. This represents an over-all six-year incidence of 36.3 per thousand in the age groups under study. The six-year incidence of coronary heart disease in the men was 54.8 per thousand as compared with 21.4 per thousand in the women. In the younger age group (30 to 44 years) there was an incidence of 1.9 per thousand in women as compared with 24.9 per thousand in men (a thirteenfold difference). In the older age group (45 to 62 at entry into the Study) this sex ratio becomes attenuated to only a twofold difference with an incidence of 90.6 per thousand in men as compared with 44.6 per thousand in women. As indicated in Table 4, 24 of the 88 men who developed myocardial infarction* died suddenly.

* All sudden deaths are considered to be myocardial infarctions.

TABLE 3B. Six-Year Incidence Rate of New CHD by Age and Sex

Age at Entry	Rate per 1,000 Population		
	Framingham Study Group	Sample Respondents	Volunteers
Men	54.8	53.6	61.9
30-44	24.9	24.1	29.8
45-62	90.6	89.1	100.7
Women	21.4	21.5	21.1
30-44	1.9	2.3	0
45-62	44.6	44.3	46.4

Of these, 15 (62.5%) had no previous evidence of CHD and this constituted the only known manifestation of the disease. Seven of the men who suffered myocardial infarction had no clinical evidence of the event other than the development of characteristic electrocardiographic evidence of infarction, and the disease would have been undetected unless periodic routine electrocardiograms were undertaken in apparently well individuals. Three of 19 women who suffered myocardial infarction manifested the disease as sudden death. All of these

occurred as the first reported manifestation of CHD.

There is clearly a difference in the predominant clinical manifestation of coronary heart disease in the sexes (Table 4). The CHD appearing in the women was predominantly angina pectoris without associated myocardial infarction (69%). This is in contrast to the men in whom angina pectoris without associated myocardial infarction constituted only 30% of the coronary heart disease developing in the six years of observation. Among all cases of

TABLE 4. Clinical Manifestations of CHD Developing in Six Years of Follow-Up

Clinical Manifestation	Number		Per Cent	
	Men	Women	Men	Women
Total CHD	125	61	100.0	100.0
Definite myocardial infarction by history and ECG*	57	14	45.6	23.0
With AP†	32	7		
Without AP†	25	7		
Definite myocardial infarction by ECG only	7	2	5.6	3.3
Sudden death	24	3	19.2	4.9
With pre-existing MI‡	3	—		
With pre-existing AP†	6	—		
Without pre-existing CHD	15	3		
Definite angina pectoris	37	42	29.6	68.8

* Electrocardiogram.

† Angina pectoris.

‡ Myocardial infarction.

TABLE 5. Mean Serum Cholesterol at Initial Examination: Comparison New CHD and Population at Risk

Age at Entry	Number		Mean		Standard Deviation of Population
	New CHD	Population at Risk	New CHD	Population at Risk	
Men					
30-34	5	375	257*	219	45
35-39	11	419	267*	222	42
40-44	14	402	259*	229	46
45-49	14	341	250*	231	37
50-54	27	338	245*	227	40
55-59	41	252	248*	229	43
Women					
40-44	3	480	316*	222	39
45-49	14	423	286*	240	48
50-54	13	403	239	250	46
55-59	24	355	260	258	48

* Significantly elevated (at the 5% level) compared with population at risk.

CHD, myocardial infarction with or without associated angina pectoris occurred as the manifestation of CHD approximately twice as frequently in the male coronary subjects as in the female. The incidence of angina pectoris in subjects with myocardial infarction, however, is about the same in the sexes.

SERUM CHOLESTEROL

The data presented here are based on determinations of serum cholesterol which were made in the Framingham Laboratory by the method of Abell, Levy, Brodie, and Kendall (8). During the period when much of the data was being collected, the laboratory standardized its results by exchange

TABLE 6. Six-Year Incidence of CHD According to Initial Serum Cholesterol Level: Ages 40-59

Serum Cholesterol (mg/100 ml)	New CHD	Population at Risk	Incidence Rate per 1,000 Population	
			Observed	Expected*
Men, 40-59	96†	1,333	72.0	70.6
Less than 210	16	454	35.2‡	69.4
210-244	29	455	63.7	70.8
245 or more	51	424	120.3‡	71.8
Women, 40-59	54†	1,661	32.5	32.7
Less than 210	8	445	18.0	25.2
210-244	16	527	30.4	31.3
245 or more	30	689	43.5	38.7

* Expected rate is calculated by applying age-sex-specific incidence rates (five-year age interval) in the Framingham Study Group to the population in the specified category of sex and cholesterol.

† Total number of new cases of CHD and the population at risk varies in different tabulations since it was not possible to obtain blood specimens on every subject.

‡ Significantly different (at the 5% level) from the expected rate.

TABLE 7A. Mean Systolic and Diastolic Blood Pressures at Initial Exam.
Comparison of New CHD and Population at Risk

Age and Sex	Number of Persons		Systolic Blood Pressure			Diastolic Blood Pressure		
			Mean		Standard Deviation, Population	Mean		Standard Deviation, Population
	New CHD	Population at Risk	New CHD	Population at Risk				
	New CHD	Population at Risk	New CHD	Population at Risk				
Men								
30-34	5	388	128	131	16	83	83	11
35-39	11	438	144*	132	17	95*	85	12
40-44	15	420	133	135	18	90	87	12
45-49	15	352	144	138	21	93*	88	12
50-54	27	353	148*	140	22	90	89	13
55-59	41	262	162*	145	27	96*	88	15
Women								
40-44	3	508	125	131	20	81	83	12
45-49	16	446	158*	142	24	97*	87	12
50-54	14	421	171*	150	30	96	90	14
55-59	24	371	178*	154	31	100*	91	15

* Significantly elevated (at the 5% level) compared with population at risk.

Note: Blood pressures are available for everyone in the Study Group. This is not true for other measures.

of serum lipids with the four laboratories participating in the Cooperative Lipoprotein Study (9).

Higher mean cholesterol levels were demonstrated among subjects who developed coronary heart disease than in the population at risk (Table 5). This indicates an association between serum cholesterol levels and the subsequent development of CHD. In men, serum cholesterol levels tended to be higher for those who subsequently developed CHD in the six years of observation than in the population at risk. This elevation was most marked for men in the youngest age group and diminished with age. Beyond age 59 there were too few persons in the Study for analysis.

The risk associated with serum cholesterol level was analyzed in men in the broad age group, 40 to 59 years at entry into the Study (Table 6). Separation of the men in the population at risk into three categories according to increasing levels of serum cholesterol yields groups of similar size when dividing points are made at levels of 210 and 245 mg per 100 ml. Analysis of

these groups reveals a gradient of risk of developing CHD with increasing levels of serum cholesterol, such that those with serum cholesterols over 244 mg per 100 ml have more than three times the incidence of CHD as do those with cholesterol levels less than 210 mg per 100 ml (Table 6). This cannot be attributed to aging within the group studied since no significant gradient of serum cholesterol with age can be demonstrated in men (Table 5). In evaluating the risk associated with elevation of serum cholesterol levels it is important to recognize that in the Framingham population the reference base for serum cholesterol (i.e., "normal" cholesterol) may be high when compared with some other populations in which lower rates of CHD have been claimed.

Since no new coronary heart disease developed in women less than 40 years of age at entry into the Study, no analysis of the association of serum cholesterol level with the risk of CHD was possible. A significant elevation of mean serum cholesterol is evident for women 40 to 49 years old who de-

TABLE 7B. Mean Systolic and Diastolic Blood Pressures at Initial Exam: Comparison of New CHD and Population at Risk, Framingham Study Group Without Left Ventricular Hypertrophy by Electrocardiogram

Age and Sex	Number of Persons		Systolic Blood Pressure			Diastolic Blood Pressure		
			Mean		Standard Deviation, Population	Mean		Standard Deviation, Population
	New CHD	Population at Risk	New CHD	Population at Risk		New CHD	Population at Risk	
Men								
30-34	4	382	128	131	15	84	82	10
35-39	11	426	144*	132	16	95*	84	11
40-44	14	407	133	135	17	90	87	12
45-49	14	336	140	137	20	91	87	11
50-54	24	337	145	139	21	90	88	13
55-59	31	238	158*	143	25	92*	87	14
Women								
40-44	3	501	125	130	19	81	83	12
45-49	15	439	157*	141	23	96*	87	12
50-54	13	397	164*	147	26	93	90	13
55-59	21	357	173*	152	29	97*	90	15

* Significantly elevated (at the 5% level) compared with population at risk.

Note: Blood pressures are available for everyone in the Study Group. This is not true for other measures.

veloped coronary heart disease but not for women 50 to 59 years old (Table 5). However, a significant (although not striking) gradient of risk with increasing cholesterol levels could be demonstrated for the entire group of women aged 40 to 59 years (Table 6).

BLOOD PRESSURE AND ASSOCIATED CHARACTERISTICS

It was evident on the basis of the four-year follow-up experience that elevation of blood pressure was associated with an increased risk of the development of CHD among men 45 to 62 years of age (1). The occurrence of additional cases of new CHD during two more years of observation permits the analysis of this factor to be extended to younger men and to women.

In Tables 7A and B are shown the mean blood pressures of the population at risk (those free of coronary heart disease at the initial examination) and of those of the group who developed CHD during the six years of observation. Among both men and

women aged 45 to 59 years on entry, blood pressures, either systolic or diastolic, were significantly higher in the group who subsequently developed CHD than in the whole population at risk. Outside of this age range, the association of elevated blood pressure levels with CHD is not consistently significant. As indicated in Table 8 progressive degrees of blood pressure elevation were associated with increased risk of the subsequent development of CHD. Hypertension associated with the electrocardiographic pattern of left ventricular hypertrophy (LVH by ECG) was associated with a higher incidence of coronary heart disease than was hypertension alone.

It was not possible on the basis of the data to assign greater importance to the diastolic than to the systolic blood pressure level as a predictor of subsequent coronary heart disease. This can be explained by the high correlation between systolic and diastolic blood pressure. Two other values of blood pressure measurement, pulse pres-

sure and systolic lability, were also considered. Both of these measures varied with the level of systolic pressure and both were higher in the coronary group than in the population as a whole. Elevation of either measure, however, did not contribute independently to the risk of subsequent CHD. As previously noted, the electrocardiographic finding of left ventricular hypertrophy is associated with an unusually high risk of the subsequent development of CHD among men age 40 to 59 years (Table 8). Within six years one-third of the men 40 to 59 years of age with this finding had developed overt CHD, as had one-fifth of these men with "possible" LVH by electrocardiogram. The relative infrequency of CHD among women and among younger men during the six years of observation precluded the demonstration of a com-

parable association among them, though the data are suggestive for older women.

Several possible explanations for the high incidence of coronary heart disease associated with left ventricular hypertrophy by ECG are suggested. It is possible that the group with this finding includes a sizable proportion with subclinical CHD at entry. This might happen if electrocardiographic evidence of LVH masked evidence of CHD in the ECG or if the electrocardiographic patterns for the two conditions could be confused. It could also happen if, in fact, the LVH pattern was an indicator of CHD. These possibilities led to a preliminary analysis excluding persons with left ventricular hypertrophy by electrocardiogram from the population at risk. The effect of this on the analysis of blood pressure can be judged by com-

TABLE 8. Six-Year Incidence Rate of CHD by Blood Pressure Category and Electrocardiogram of Left Ventricular Hypertrophy: Ages 40 to 59

Sex, Hypertensive Status, ECG Evidence of LVH*	Number of Persons		Incidence Rate per 1,000 Population	
	New CHD	Population at Risk	Observed	Expected
Men, 40 to 59	98	1,387	70.7	70.7
Normotension	23	556	41.4	68.8
Borderline hypertension	38	532	71.4	68.6
Definite hypertension	37	299	123.7	77.8
Definite hypertension and ECG evidence:				
No LVH	27	265	101.9	75.8
Possible LVH	3	15	200.0	78.4
Definite LVH	7	19	368.4	105.1
Women, 40 to 59	57	1,746	32.6	32.6
Normotension	6	704	8.5	26.5
Borderline hypertension	20	647	30.9	35.0
Definite hypertension	31	395	78.5	39.8
Definite hypertension and ECG evidence:				
No LVH	26	357	72.8	40.0
Possible LVH	1	19	52.6	34.6
Definite LVH	4	19	210.5	42.2

* Left ventricular hypertrophy.

Note: Expected rate is calculated by applying the age-sex-specific incidence rates (in five-year age intervals) of the Framingham Study Group to the population in the specified sex-hypertension LVH category.

TABLE 9. Mean Systolic and Diastolic Blood Pressures According to Presence or Absence of ECG Evidence of LVH at Initial Examination: Men Aged 45 to 62

ECG Evidence of LVH	New CHD	No CHD
Mean Systolic Pressure		
Total	154	140
Definite or possible LVH	171	162
No LVH	149	139
Mean Diastolic Pressure		
Total	93	87
Definite or possible LVH	100	98
No LVH	91	87
Number of Men Aged 45-62		
Total	94	943
Definite or possible LVH	18	45
No LVH	76	898

paring the results displayed in Table 7A with those in Table 7B. There is a very slight reduction in the association between CHD and blood pressure when the group having LVH by ECG is excluded from the analysis. In general, the omission of this group from the analysis of the factors related to the development of coronary heart disease under consideration in this paper had only a minor effect.

Another possibility which may explain the association of left ventricular hypertrophy by electrocardiogram with the development of CHD is a strong inter-relationship between the electrocardiographic pattern and hypertension. The electrocardiographic abnormality may well reflect either long standing or severe degrees of hypertension. Among the men without LVH by ECG, those who developed coronary heart disease had blood pressures which were higher on the average by 10.4 mm systolic and by 3.9 mm diastolic compared with those who did not develop CHD (Table 9). A similar elevation of blood pressure in those who developed CHD is found within the group of men with definite or possible LVH by ECG. This indicates that blood pressure is asso-

ciated with the risk of developing coronary heart disease independently of the presence or absence of left ventricular hypertrophy by electrocardiogram.

Whether left ventricular hypertrophy by electrocardiogram is associated with the risk of developing coronary heart disease independently of blood pressure levels is not as easily evaluated. Blood pressures are much higher in the small group with LVH by ECG than in those without it, and this in itself should enhance the risk of developing CHD. How much of the excess risk associated with the electrocardiographic finding is accounted for by elevated blood pressure is difficult to judge because of the small number of cases and because of the large sampling variability in incidence rates among men with this electrocardiographic finding. However, reference to Table 10 indicates the effect of left ventricular hypertrophy by electrocardiogram in blood pressure diagnostic categories. It can be seen that at each diagnostic blood pressure category, the presence of LVH by ECG is associated with an excess incidence of coronary heart disease. Left ventricular hypertrophy by ECG appears to make an

TABLE 10. Six-Year Incidence of CHD According to Hypertensive Status and ECG Evidence of LVH at Initial Exam: Men Aged 40 to 59

Hypertension	LVH Present	LVH Absent
Incidence Rate per 1,000		
None	200.0	38.5
Borderline	120.0	69.0
Definite	294.1	101.9
New CHD		
None	2	21
Borderline	3	35
Definite	10	27
Population at Risk		
None	10	546
Borderline	25	507
Definite	34	265

Note: LVH means definite or "possible" left ventricular hypertrophy.

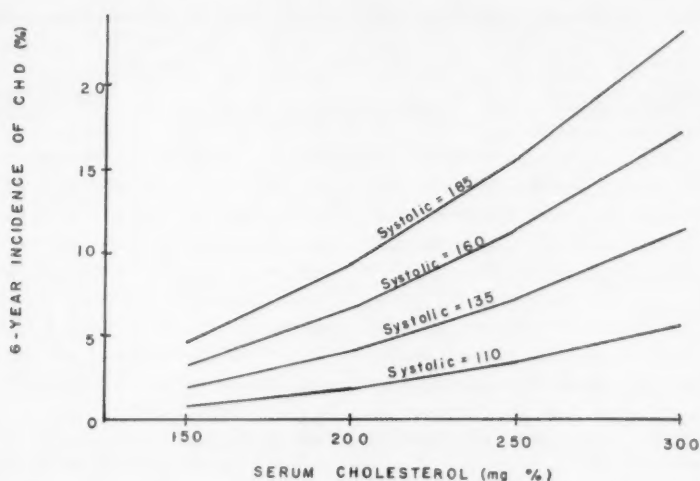


FIGURE 1. Six year incidence of coronary heart disease according to serum cholesterol levels at specified systolic blood pressures (men 45 to 62 years). These curves are based on the following assumptions: (1) The joint distribution of the logarithms of blood pressure value minus 75 and cholesterol value is bi-variate normal within both the coronary heart disease and non-coronary heart disease groups; (2) The variance-covariance matrices in the coronary heart disease and non-coronary heart disease groups are equal (14).

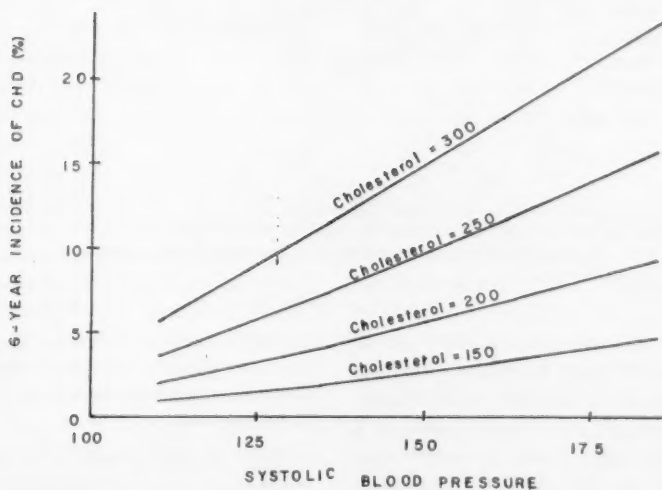


FIGURE 2. Six-year incidence of coronary heart disease according to level of systolic blood pressure at specified serum cholesterol levels (men 45 to 62 years). For explanation, see legends for Figure 1.

TABLE 11. Six-Year Incidence of CHD, According to Combinations of Blood Pressure, Serum Cholesterol, and ECG Evidence of LVH at Initial Exam: Ages 40-59

Sex and Combinations of Blood Pressure, Serum Cholesterol, and ECG Evidence of LVH	Population at Risk		New CHD	Incidence Rate per 1,000 Population	
	Number	Per Cent		Observed	Expected
Men, 40 to 59	1,333	100.0	96	72.0	70.6
Normal* on all three	811	60.8	29	35.8	67.5
Abnormal* on one only	416	31.2	43	103.4	73.6
Blood pressure	186	14.0	17	91.4	76.8
Cholesterol	207	15.5	25	120.8	70.4
LVH	23	1.7	1	43.5	76.4
Abnormal* on two only	98	7.4	20	204.1	81.4
BP and cholesterol	65	4.9	10	153.8	74.1
BP and LVH	25	1.9	6	240.0	87.7
Cholesterol and LVH	8	0.6	4	500.0	121.4
Abnormal* on all three	8	0.6	4	500.0	102.9
Abnormal* on two or three	106	8.0	24	226.4	83.0
Women, 40 to 59	1,661	100.0	54	32.5	32.7
Normal* on all three	888	53.5	15	16.9	27.2
Abnormal* on one only	597	35.9	24	40.2	38.1
Blood pressure	206	12.4	14	68.0	38.0
Cholesterol	382	23.0	10	26.2	38.2
LVH	9	0.5	—	0	37.9
Abnormal* on two only	162	9.8	13	80.2	42.1
BP and cholesterol	134	8.1	10	74.6	43.3
BP and LVH	23	1.4	3	130.4	35.8
Cholesterol and LVH	5	0.3	—	0	39.5
Abnormal* on all three	14	0.8	2	142.9	42.7
Abnormal* on two or three	176	10.6	15	85.2	42.2

* Abnormal blood pressure is defined as definite hypertension, abnormal cholesterol is a serum cholesterol reading of 260 mg/100 ml or higher, and abnormal LVH is a diagnosis of possible or definite LVH on the electrocardiogram. "Normal" means not abnormal; it includes normotension and borderline hypertension, serum cholesterol less than 260 mg/100 ml, no LVH by ECG.

independent contribution to the risk of development of CHD, increasing the risk of development of coronary heart disease two to threefold when blood pressure is held constant. Because of the small numbers it was necessary to examine the broad age group 40 to 59 years in men and hence it is not possible to assess completely the possible effect of age.

INTERACTION OF HYPERTENSION, HYPERCHOLESTEROLEMIA, AND THE ELECTROCARDIOGRAPHIC PATTERN OF LEFT VENTRICULAR HYPERTROPHY

Data already presented indicate that hypertension, hypercholesterolemia, and the electrocardiographic pattern of left ventricular hypertrophy are each associated with an increased risk of the development

of CHD in men 40 to 59 years of age. It has been previously shown (1) that there is almost no correlation between serum cholesterol level and diastolic or systolic blood pressure. Left ventricular hypertrophy by ECG is strongly associated with hypertension, and has been shown to contribute to risk of development of CHD (Tables 8 and 9). At each level of blood pressure in hypertensives the presence of LVH is associated with a two to threefold increase in incidence of CHD (Table 10). Consequently each of these characteristics would be expected to contribute to the risk of development of CHD and combinations of these factors could be expected to augment the risk. From Figures 1 and 2 it can be seen that the incidence of CHD does indeed rise progressively with increasing levels of both blood pressure and serum cholesterol and that a combination of these two factors further augments the risk. In Table 11 the six-year incidence of coronary heart disease in persons having various combinations of these three characteristics is given. Men aged 40 to 59 years, normal in all these characteristics, had a six-year incidence of CHD of only 35.8 per thousand. When abnormal with respect to one of these characteristics the risk almost tripled (103.4 per thousand). If abnormal in two of these characteristics the six-year incidence climbs to 204.1 per thousand, approximately doubling the risk associated with abnormality in one characteristic. Abnormality in all three characteristics probably again doubles the incidence, but because of small numbers available and sampling variability, it is not possible to assess this risk reliably. Abnormality of two or more of these risk characteristics is associated with a six-year incidence of 226.4 per thousand. Approximately the same magnitude of compounding of risk associated with these characteristics (hypertension, hypercholesterolemia, and the ECG pattern of left ventricular hypertrophy) is seen in women 40 to 59 years of age. The incidence rates

are generally lower, women normal in all three characteristics having an incidence of 16.9 per thousand, rising to 40.2 per thousand when abnormal in only one characteristic, and doubling to 80.2 per thousand when two abnormal characteristics are present. When two or more factors are abnormal, a six-year incidence of 85.2 per thousand is noted.

These risk characteristics are found with some frequency in the population: 39% of men and 46% of women 40 to 59 years of age have at least one of these abnormal characteristics, while 8% of men and 11% of women have two or more of these abnormal characteristics.

DISCUSSION

The rarity of coronary heart disease in the younger female (two per thousand) is in sharp contrast to the incidence of this disease in the male of the same age (25 per thousand) as indicated in Table 3B. This sex differential is greater than the differences in incidence produced by any other factor thus far investigated in this disease. Clearly, any statement regarding the etiology of CHD will have to explain the sex ratio. This also indicates a fruitful area for research into the pathogenetic mechanism of this disease. The gap between the sexes closes after age 45 so that only a twofold difference exists. This strongly suggests, among other things, an endocrine influence related to the menopause.

Not only the incidence, but the clinical manifestation of CHD appeared to differ markedly in the sexes (Table 4). Coronary heart disease in the female is manifested chiefly as angina pectoris. Seventy per cent of all CHD occurring in females exhibited this manifestation. In the male, on the other hand, the disease is manifested chiefly as myocardial infarction or sudden death with only 30% exhibiting angina pectoris alone. The percentage of sudden death in men (19.2%) greatly exceeded that in women (4.9%). Myocardial infarction was

approximately twice as frequently exhibited by men. It thus appears that the seriousness of the disease developed in the two sexes as well as the incidence differs markedly.

On the basis of clinical studies it is commonly believed that angina pectoris occurs predominantly in males (10). Data presented in Table 4 indicate that if all cases of angina pectoris occurring in a community are considered, rather than only those presenting themselves for medical care, angina pectoris is as common in the female as in the male. In six years of follow-up of persons initially free of CHD 124 cases of angina pectoris developed. In 79 instances this occurred alone, in 39 instances the angina was associated with myocardial infarction, and in six instances it antedated sudden death. Of the 79 instances of angina pectoris unassociated with myocardial infarction 42 occurred in women (53.2%), while of the 39 cases of angina pectoris associated with myocardial infarction only seven were in women (17.9%). Forty per cent of all angina encountered in the study population occurred in women. Angina pectoris in association with myocardial infarction was more common in men.

It is widely accepted that sudden death (occurring within a matter of minutes) is usually the result of coronary heart disease with or without coronary occlusion (11). This is especially likely if other possible causes such as aortic valvular deformity, pulmonary embolism, and aortic dissection or rupture can be excluded. Examination of the Framingham Study subjects prior to the event and careful evaluation of the circumstances under which the sudden death occurred renders it unlikely, although still possible, that these other etiologies were responsible for the deaths. It is recognized that sudden death may be the only manifestation of CHD (11). It has not been possible up until now, however, to determine how often sudden death occurs as the ini-

TABLE 12. Immediate Mortality Following Initial Myocardial Infarction: Men in Framingham Study Group

	Total	Survived*	Died within Three Weeks
Hospitalized	49	43	6
Not hospitalized	39	19	20†
Total	88	62	26

* Known living up to time of report or died of other causes after two-year survival. All survivals in excess of two months.

† All sudden deaths.

tial manifestation of CHD. In the six years of observation of men in the Framingham Study group, 24 sudden deaths occurred. Nine (37.5%) of these had pre-existing evidence of coronary heart disease (six had angina pectoris and three had myocardial infarction). Thus 62.5% of all sudden deaths attributed to CHD in men occurred as the initial manifestation of the disease.

It can be seen from Table 12 that there is a high immediate mortality associated with myocardial infarction. For purposes of this discussion sudden death is classified as myocardial infarction. Of 88 cases of myocardial infarction in men occurring in the six years of observation, 26 (29.5%) died within three weeks of the initial infarction. Indeed, 20 of the 26 (77%) deaths within three weeks were sudden, occurring in a matter of minutes.

It is also noteworthy that approximately 45% of those with the initial myocardial infarction never got hospitalized. Of these, one-half never had the opportunity to be hospitalized because of the occurrence of sudden death. Approximately 25% of those not hospitalized had unrecognized infarctions discovered only because of routine electrocardiographic studies on biennial examinations. Thus approximately 70% of the initial infarctions not hospitalized in the community never had the opportunity to be hospitalized in order to receive the

benefits of therapeutic medicine. Indeed, the majority of these could not even be seen by a physician prior to their demise. Of the 49 who survived to enter a hospital, six (12.2%) died shortly after admission (only one survived more than ten days). As indicated previously 15 of the 24 (62.5%) sudden deaths which occurred had no prior evidence of coronary heart disease. These data suggest to the authors that in efforts to control CHD, major emphasis must be placed on prevention.

Six years of follow-up experience in the longitudinal prospective study of coronary heart disease in Framingham have confirmed the widely recognized influence of hypertension and hypercholesterolemia on the development of CHD. These factors have been noted in clinical studies to occur in excess in persons with coronary heart disease, and in animal experiments to be associated with the development of atherosclerosis. It is now demonstrated that these factors *precede* the development of overt CHD in humans and are associated with increased risk of the development of CHD. The association of these factors with the subsequent development of coronary heart disease has been independently demonstrated in other longitudinal studies (12, 13). In addition, it is now demonstrated that the electrocardiographic pattern of left ventricular hypertrophy is also associated with increased risk of developing CHD.

It is now possible to assess the magnitude of the increase in risk associated with these characteristics. It can be seen from Table 8, by comparing the ratios of observed to expected incidence rates, that hypertension, as defined, is associated with a 2.6-fold increase in risk of development of CHD in men 40 to 59 years of age and a sixfold increase in women in the same age. This represents a considerable increase in risk. Of interest also is the comparison of risk in the sexes. It is often stated that women tolerate hypertension better than do men.

Insofar as the relationship between hypertension and coronary heart disease is concerned, the six-year incidence figures do not support this thesis. If the independent contribution of hypertension to risk is assessed by holding the other factors which contribute to risk constant (i.e., left ventricular hypertrophy by electrocardiogram and elevated serum cholesterol), then, of the three characteristics under consideration, hypertension represents a greater relative increase in risk in women than in men although the absolute incidence of CHD in women never reaches that of men in any category (Table 11). Elevation of serum cholesterol level (i.e., 245 mg per 100 ml or more) is associated with more than a threefold increase in risk in men aged 40 to 59, while in women of the same age a 1.6-fold increase is noted (Table 6). As seen in a comparison of Table 6 and Table 8, and in Table 11, when blood pressure and left ventricular hypertrophy factors are removed from consideration, the independent contribution of cholesterol (at slightly higher levels of 260 mg per 100 ml or greater) to risk in women is further reduced so that cholesterol levels contribute only slightly to the increased risk among women but very significantly among men. Some of the increased risk is undoubtedly attributable to a higher mean age of women with higher cholesterol level, since cholesterol increase with age occurs to a greater extent in women than in men. It thus appears that, in assessing the contribution to risk of developing CHD, of the three factors under consideration, hypertension represents a greater risk factor for women than for men, whereas for serum cholesterol levels the converse is true, cholesterol contributing only slightly to the increased risk among women, but very significantly increasing risk among men.

Combinations of the three risk factors under consideration appear to augment further the risk of subsequent development of coronary heart disease. It has been dem-

onstrated (Figures 1 and 2 and Table 11) that the incidence of coronary heart disease rises progressively as these factors are combined.

There can be no doubt that absence of these characteristics is distinctly advantageous since such persons demonstrate a relatively low risk of developing CHD. Whether or not the correction of these abnormalities once they are discovered will favorably alter the risk of development of disease, while reasonable to contemplate and perhaps attempt, remains to be demonstrated.

As additional longitudinal observations are made, it is hoped that additional risk factors will be determined. This will allow further identification of susceptible individuals and hopefully suggest methods of control.

SUMMARY AND CONCLUSIONS

A six-year longitudinal study is reported of a stratified random sample of the population of Framingham, Massachusetts, aged 30 to 59 years, covering factors related to the development and clinical manifestations of coronary heart disease. The factors studied include blood pressure, serum cholesterol levels, and certain electrocardiographic abnormalities. Follow-up of the study group free of CHD at the initial examination has been reasonably complete.

One hundred and eighty-six men and women aged 30 to 59 years on entry into the study developed coronary heart disease in the six years of observation, representing an over-all six years' incidence of 36.3 per thousand. In the younger age group, 30 to 44 years, a male to female ratio of 13 to 1 was noted. In the older age group, 45 to 62 years, this sex ratio became attenuated to only a twofold difference.

In addition to incidence, the clinical manifestations of CHD were noted to differ markedly in the sexes. Coronary heart disease in the female was noted to be manifested chiefly as angina pectoris (70%). In

the male, the disease was manifested chiefly as myocardial infarction or sudden death, with only 30% exhibiting angina pectoris alone. The incidence rate of sudden death was ten times as common in men (10.5 per 1,000) as in women (1 per 1,000) and the incidence rate of myocardial infarction was five times as high in men. Contrary to general belief, uncomplicated angina pectoris was noted to occur as frequently in women as in men; 53% of all such angina pectoris developing in the population occurred in women. Only angina pectoris in association with myocardial infarction was noted to be more common in men.

It has been noted that 62.5% of all sudden deaths attributed to coronary heart disease in men occurred as the initial manifestation of the disease. A high immediate mortality was noted to be associated with myocardial infarction. Of 88 cases of myocardial infarction in men, 26 (29.5%) died within three weeks of the initial infarction. Of those with initial myocardial infarction 44% were not hospitalized, half of these because of the occurrence of sudden death. Another 23% of those not hospitalized had infarctions that were unrecognized. Thus three of four initial infarctions not hospitalized in the community could not have been hospitalized owing to sudden death or unrecognized infarction. Of those who survived to enter a hospital, 12.2% died shortly after admission.

The well-recognized influence of hypertension and hypercholesterolemia on the development of coronary heart disease is confirmed. It is now demonstrated that these factors precede the development of overt CHD and are associated with increased risk of its development. In addition, it is now demonstrated that the electrocardiographic pattern of left ventricular hypertrophy is also associated with increased risk of developing CHD.

The magnitude of the increase in risk associated with these characteristics has been assessed. Hypertension has been noted

to be associated with a 2.6-fold increase in risk in men 40 to 59 years of age and a six-fold increase in women the same age. With respect to the development of coronary heart disease, hypertension was noted to represent a greater risk factor in women than in men, while elevated serum cholesterol levels contributed only slightly to increased risk among women as compared with men. Elevation of serum cholesterol levels (i.e., 245 mg per 100 ml or more) was associated with more than a threefold increase in risk among men aged 40 to 59 years.

A pattern of left ventricular hypertrophy by electrocardiogram was noted to be associated with a two or three-fold increase in risk of development of CHD at given hypertensive blood pressure levels in men. Combinations of these risk factors (hypertension, elevated serum cholesterol level, and left ventricular hypertrophy by electrocardiogram) were noted to augment further the risk of development of CHD. Men 40 to 59 years of age, lacking these three abnormal characteristics, were noted to have a six-year incidence of coronary heart disease of 35.8 per thousand. When all of these characteristics were present the incidence rose to approximately 500 per thousand. These risk characteristics were shown to occur with sufficient frequency in the population to merit concern, 8% of men and 11% of women having two or more of these abnormal characteristics. At least one abnormal characteristic was present in over 40% of the population aged 30 to 59 years.

SUMMARIO IN INTERLINGUA

Un specimen de 5.127 subjectos de etates de 30 a 59 annos, le quales initialmente esseva libere de morbo cardiac coronari, esseva observate durante sex annos. In le curso de iste intervallo, 125 masculos e 61 feminas disveloppava manifestationes de morbo cardiac coronari. Inter le 34 casos in le gruppo de etates ab 30 ad 44 annos, le proportion masculine a feminin de incidentia esseva 13 a 1. Inter le

152 casos in le gruppo de etates ab 45 ad 62 annos, le proportion masculine a feminin de incidentia esseva approximativemente 2 a 1. Le incidentia de angina de pectore esseva plus o minus equal pro le duo sexos. Tamen, infarcimento myocardial esseva duo vices plus commun in masculos e morte subite dece vices.

In masculos, un alte mortalitate immediate (30%) esseva associate con infarcimento myocardial initial (incluse mortes subite). Quarantacinque pro cento de 88 masculos suffrente infarcimento myocardial non esseva hospitalisate, primarimente a causa del facto que morte superveniva subitementemente o que le infarcimento myocardial non esseva recognoscite como tal.

Factores de risco esseva evalutate in le gruppo de etates inter 40 e 59 annos. Hypertension (160/95 mm de Hg o plus) esseva associate con un quasi triplice augmento del risco in homines e un sextuple augmento in feminas. Elevation del nivello seral de cholesterol (245 mg per 100 ml o plus) esseva associate con un augmento plus que triplice del risco in masculos, durante que illo contribuiva paucio (o nihil del toto) al augmento del risco in feminas. Le configuration electrocardiographic de hypertrophia sinistro-ventricular esseva associate con un augmento duplice o triplice del risco de un disveloppamento de morbo cardiac coronari.

Combinations del tres characteristicas resultava in un augmento progressive in le risco de disveloppamento morbo cardiac coronari, durante que subjectos libere de omne le mentionate anormalitates disveloppava le morbo a un prorata de solamente un medietate de illo del population total de iste studio. Le anormalitates occurreva in le population con un frequentia sufficientemente alte pro meritar nostre sollicitude.

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Population Studies of Atherosclerosis

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THE POPULATIONS OF NATIONS having widely different civilizations, or of contrasting groups or races within nations, afford great natural laboratories for studies of arteriosclerosis and of the net effects produced by differences in diet, living habits, climate, stress, and other variables. This unique opportunity to study the disease in the human has brought forth from many parts of the world one of the largest accumulations of data in medical history. From it has come a new awareness of the scope and gravity of the problem. Vital statistics and the statistical approach in general have attained a new eminence in medicine because of the awesome numbers of cases with which they deal—many-fold those of a clinician's lifetime.

The contributions of population studies to our knowledge of atheromatous disease have been incalculable. What is perhaps the major advance in approach in recent decades—the concept that atherosclerosis is in fact a disease rather than an inevitable consequence of aging—is based largely on such statistical evidence. Probing of the statistics for etiological clues has yielded some promising leads, even a little humor.*

Received for publication December 30, 1960.

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The studies of Haitian and American Negroes reported herein were supported by grants from the National Heart Institute (H4085) and the South Carolina Heart Association.

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* E.g., taking into account a number of studies and statistical reports, this "Thumbnail Sketch of the Man Least Likely to Have Coronary Heart Disease" (1):

While it may be true that such data have been utilized at times to prove preconceived ideas (always a pitfall in statistical interpretation) or have served seemingly to indict the diet or living habits of entire nations of people and of civilization itself, they have provided an almost unprecedented stimulus and guidance for investigation.

Human studies, uncontrolled as they necessarily are and fraught with an appalling number of variables, lack the precision and niceties of supervised experiments in the animal laboratory. On the other hand, they do deal with the end results, in terms of the net effects in the human. They do serve as nothing else can to define the problem on a world-wide scale and to elucidate the natural history of a disease.

The purpose of this review is to sketch the main currents of human population studies of atherosclerosis and to summarize briefly their methods and results, their contributions and limitations, the evidence pro and con. This is perhaps best accomplished by selecting from the various ap-

An effeminate municipal worker or embalmer,
Completely lacking in physical and mental alertness
and without drive, ambition or competitive spirit
who has never attempted to meet a deadline of any kind.

A man with poor appetite, subsisting on fruit
and vegetables laced with corn and whale oils,
Detesting tobacco,

Spurning ownership of radio, TV, or motor car,
With full head of hair and
Scrawny and unathletic in appearance,

Yet constantly straining his puny muscles by
exercise;

Low in income, B.P., blood sugar, uric acid, and
cholesterol,

Who has been taking nicotinic acid, pyridoxine,
and long term anticoagulant therapy

Ever since his prophylactic castration.

proaches a few examples which might be considered representative, or which seem to afford provocative leads in a rapidly growing field of investigation.

CLINICAL OBSERVATIONS AND VITAL STATISTICS

During the half century which has followed the first experimental production of atheromatous lesions in the arteries of animals, surveys based mainly on clinical diagnoses and vital statistics have indicated that atherosclerosis in its various manifestations, now ranked first among the causes of death in the United States, may have a vastly lower incidence among certain other peoples of the world. It has been reported to be conspicuously lower among some primitive tribes in Africa, and lower in some population groups of Italy, Spain, and Greenland, where fats assertedly comprise a smaller proportion of the diet than they do in the United States. Similar surveys have contended that the atheromatous diseases are extremely rare among Orientals who subsist largely on vegetarian diets, that the observed incidence of clinical manifestations of coronary disease declined markedly in European countries during periods of relative famine incident to World War II, and that, conversely, populations subsequently exposed to more plentiful diets showed the reverse trend. All this statistical evidence has been extensively reviewed and summarized in the medical literature (2-4).

Inasmuch as cholesterol had long since been identified as the chief chemical constituent of the arterial lesions and because comparable lesions could be produced in certain animals by feeding them diets high in cholesterol, attention was directed primarily toward that constituent of the human diet. Correlations of kinds and amounts of dietary fats with incidence of atherosclerosis became the rule. Furthermore, vital statistics of the United States and other countries indicated that the coronary and perhaps other manifestations of

atherosclerosis may be rapidly increasing among the more highly civilized populations of the world, and even among the animals in our zoos (5). The concept has grown that the relatively high fat content of diets of the peoples living under an economy of abundance causes high levels of lipids in the blood, which in turn cause the occlusive lesions in the intima of arteries. Certainly the evidence is irrefutable that cholesterol and other lipids are intimately involved in the genesis of the disease. But whether they are the cause, only the *modus operandi*, or perhaps only a manifestation or a result of the disease is less certain.

Illustrative of this approach are surveys carried out among Japanese, Americans, Bantus, Scandinavians, and Hawaiians which purported to show a virtually straight-line relationship between the percentage of calories in the diet derived from fat and the levels of cholesterol and other lipids in the blood (6). "While these findings do not constitute proof of the hypothesis [that the etiology of coronary disease is dominated by the long-time effect of a rich, fatty diet and an endless succession of fat-loading meals] the findings are consistent, in detail, with the theory." However Eskimos, whose diets are notoriously high in animal fat, appeared to be an exception with their normal levels of cholesterol and lipoproteins in the serum and remarkably little cardiovascular disease as judged by clinical examination (7).

The next step, that of correlation of abnormally high levels of blood lipids with severity of atherosclerosis, requires time, for plaques develop over many years, and observations of an individual's blood chemistry at a stage when overt occlusive disease is manifest are not necessarily representative of his entire life span. An additional problem in the human studies is that there are as yet no "normal controls," because we have no reliable criteria for determining who is and who is not devel-

TABLE 1. Death Rates for Men Aged 55 to 59 Years and Environmental Factors for 20 Countries (9)

Country	Death Rate per 100,000*	Average Total Daily Calories†	Fat Components as % of Total Calories				Telephones per 100 Population
			Total Fat	Satu- rated	Un- saturated	Animal Protein	
United States	704.7	3,070	39.2	33.5	5.7	8.2	35.8
Australia	577.4	3,160	37.9	34.7	3.2	7.3	18.5
Austria	293.9	2,820	31.3	23.9	7.4	5.8	7.7
Belgium	250.1	2,980	35.0	24.4	10.6	5.7	10.6
Canada	588.3	3,130	38.0	35.0	3.0	8.0	27.6
Ceylon	103.4	1,980	15.2	11.8	3.4	2.2	0.3
Chile	267.3	2,490	19.8	12.0	7.8	4.3	2.2
Denmark	294.8	3,370	38.3	25.5	12.8	6.1	20.5
Finland	621.7	3,170	31.1	28.4	2.7	6.8	11.3
France	109.9	2,850	29.5	20.7	8.8	6.4	7.6
German Federation	313.7	2,950	35.6	23.0	12.6	5.6	8.3
Italy	226.8	2,550	22.3	10.5	11.8	3.6	5.4
Japan	122.5	2,005	7.9	1.4	6.5	2.6	3.8
New Zealand	525.7	3,370	39.8	37.6	2.2	8.2	25.6
Norway	248.8	3,130	38.0	17.0	21.0	6.4	17.8
Portugal	107.7	2,560	24.5	9.4	15.1	3.9	3.2
Sweden	294.6	3,070	39.4	28.3	11.1	7.3	31.5
Switzerland	273.0	3,100	33.6	23.6	10.0	6.6	25.5
United Kingdom	427.5	3,270	38.4	35.0	3.4	5.9	14.0
Yugoslavia	68.2	2,525	19.1	13.2	5.9	2.8	1.0

* ISC category B-26 (atherosclerotic and degenerative heart disease).

† Food and Agricultural Organization of the United Nations.

oping arterial lesions which will ultimately prove fatal until the disease has almost completely run its course. Nevertheless, impressive correlations can be derived from measurements of various lipid constituents of the blood of patients with and without clinical indications of, e.g., myocardial infarction (8a, b).

A disquieting feature of some of the parallelisms which have been cited in mass statistics of diet and mortality rates from heart disease is pointed up in Table 1 (9), taken from the Annual Epidemiologic and Vital Statistics of the World Health Organization. Granting considerable error in estimation of these factors in many of the countries, the parallelism between the number of telephones per 100 population and the cardiac death rate is even more striking than that of any of the dietary

factors. Behind what may seem an obvious correlation is a bewildering complexity of associations and intercorrelations between factors which might ordinarily be thought independent. True, telephones reflect economic status, are characteristic of the more abundant life and hence of a more bountiful table laden with the fats of the land in most countries, and communication is a fair index of what we choose to call "modern progress." But they are also inextricably bound up with numerous other differences in way of life of these peoples of many races: the tempo, mechanization, educational advantages, and with accuracy of vital statistics themselves. The human tendency to see in such data only that which we look for doubtless accounts for many of the conflicting views derived from them.

Vital statistics, hospital diagnoses, and even autopsy reports from different countries can have little meaning unless considered with them are the obvious differences among nations in methods of compiling medical statistics, in numerical ratios of physicians-to-population, in the medical training, practices, and diagnostic thresholds of those physicians for the disease under study. A nation's public health facilities, its conventions relating to medical care, examinations for attendance at school, employment, insurance, etc., and the availability of specialized diagnostic procedures such as the electrocardiogram obviously have a very real bearing on its medical records. Likewise, gross inequalities between populations in the educational level of the people may be reflected in clinical statistics. The greater the contrast in civilizations, the more formidable the barriers of language, customs, and mutual understanding, the greater the importance these factors assume.

Without more than a casual knowledge of a country and its people it is difficult indeed to evaluate its medical records; even more precarious is a comparison of them with records from another "unknown." The United States, for example, leads the list among countries in numbers of deaths from coronary disease, but ranks very low in the category "other diseases of the heart" (10). Compare this with Haiti's total of five admissions in one year to all hospitals and dispensaries of the Republic for "*maladies des artères coronaires et angina de poitrine*," 266 for valvular heart disease, 298 for all other cardiac maladies, and 395,181 for infectious and parasitic diseases (11). Such is the urgency of medical problems among many peoples of the world who live under an economy of scarcity. One can appreciate why the number of clinical diagnoses of coronary disease in such an exigency is not a measure of its actual prevalence. And one need not look beyond the comparatively

well documented medical records of the United States to appreciate how much our diagnostic resources and acumen for cardiovascular disease have evolved since patients died of "dropsy," "old age," "mortification," and "acute indigestion" only a few decades ago. Understandably, the statistical incidence of coronary occlusion is increasing, and "The diseases of the present have little in common with the diseases of the past save that we die of them."

Added to the high degree of variability and distortions in the medical records themselves is the variability of interpretation from one observer to the other. One may find in India a close parallelism between economic status, dietary fat, and serum cholesterol levels in the upper socioeconomic classes (12), while another observer there finds among the same classes no evidence to support the idea that dietary fat plays a significant role in causation of coronary disease or that vegetarians or nonsmokers are less prone to develop the disease (13). Individual interests and views of investigators almost inevitably affect their interpretations of such complex mass data, yet the raw data convey little information unless digested into some sort of meaningful conclusions. One conclusion which is almost inescapable from the rapidly mounting accumulation of these statistical studies, however, is that there is a far greater need for reliable, valid statistics which are truly representative of the various populations than there is for their interpretation.

THE RACIAL FACTOR

That many of the reported differences in prevalence of atherosclerosis between countries are attributable in large part to genetically determined factors is indicated by studies of different racial groups within the same country. Significant racial differences—both physiological and pathological—have long been recognized (e.g., in scar tissue formation. in congenital diseases such

as sickle cell anemia, even in predisposition to certain infections such as tuberculosis), but that factor has been frequently neglected and misinterpreted in atherosclerosis. Major difficulties here have been the intermixture of races, often beyond definition, and the cultural, economic, and other environmental factors which are almost inevitably associated with one's race. The vastly higher incidence of syphilitic heart disease among Negroes than whites in the United States, for example, is not generally construed as evidence of their greater susceptibility to that infection.

There is a basic, unmistakable theme in nearly all comparisons which have been made between whites and Negroes as regards coronary heart disease. It is reflected in the clinical, blood lipid, and mortality statistics from South Africa, which show vast differences between Europeans, "Cape Colored," and Bantus living in the same area (14), with the latter reported to be singularly free of the disease. Essentially the same racial distinctions have been described in routine electrocardiograms from South Africa, where the Europeans were said to have twice as many infarction patterns in their tracings as the Cape Colored, who in turn had more than seven times the incidence of the Bantus (15), though it is worthy of note that many more of the Europeans on whom electrocardiograms were made were over the age of 50.

Pathologic data have disclosed racial differences which are much less impressive. In 1,250 autopsies in Hawaii no significant difference was noted between Orientals and Caucasians before the age of 45, although atherosclerosis was distinctly more prevalent among Caucasians after that age (16). A review of records of more than 4,000 autopsies in Calcutta, India indicated the maximal incidence of the disease to be in the fourth decade of life among the Indians and in the fifth decade among Europeans in the series (17). Pathologically the celebrated Bantu does not show the immu-

nity his clinical records suggest; still, it is remarkable to find any coronary arteries of African adults "without the slightest trace of atheroma . . . with stretchable smooth gray intima compared with the unyielding ochrous intima of specimens from like-aged Europeans" (18).

Public health and other medical facilities in the United States may well reduce exaggerated differences which might otherwise be described entirely to race by providing a greater equality in sanitation, medical care, and records of morbidity and mortality. Myocardial infarction has been said to be about twice as prevalent among the whites as among the Negroes in the United States (19, 20) or, expressed another way, the progression of coronary sclerosis in the Negro is said to lag ten years behind that in the white race during middle life and beyond (21). Reports of certain histologic differences in the atheromatous lesion described in some of these interracial studies (earlier fraying and fragmentation of the internal elastic lamella, with earlier calcification in the white race [21], and a greater amount of phagocytized lipids in the stroma of plaques of Americans as contrasted to Orientals [22]) await confirmation.

The idea that various blood coagulation factors might play a causative role in the formation of atheromatous lesions is not new. More than a century ago it was suggested that deposition of fibrin on the arterial intima might be the initial lesion of atherosclerosis, a concept which is being re-examined in recent years with the resurgence of interest in the thrombotic aspects of vascular occlusion. Thrombosis, of course, is known to occur in histologically normal blood vessels. Moreover a large proportion of patients with demonstrable coronary heart disease—as many as 50% or more, depending upon one's criteria—show no demonstrable abnormality of the lipid constituents of the blood. These observations, coupled with the com-

mon failure of experimentally produced lesions in animals to progress to the final stage of thrombotic occlusion, have focused new interest on the blood clotting mechanisms and anticoagulants, an approach with obvious therapeutic implications. It also has been investigated in the Bantu, who is reported to have a generally lower level of plasma prothrombin and "better prothrombin consumption and higher plasma levels of antihemophilic globulin" than age-matched groups of healthy urban white men (23). Fibrinolytic activity was observed to be accelerated in the healthy Bantu subjects. The hypothesis is that a dynamic equilibrium may exist between the mechanism of fibrin deposition and that of fibrinolysis; and that possibly, when fibrinolysis is inhibited, unrestricted deposition of fibrin in the intima may result and thereby promote atherogenesis. Again, reasonable doubts are raised as to how much of this observed discrepancy between the races is actually due to genes and how much to dietary or other environmental attributes of the races.

THE PATHOLOGICAL APPROACH

Evaluation of the incidence of atherosclerosis in a population by making a study of autopsy material is perhaps less fraught with variables of perception and judgment than is a purely clinical appraisal. Moreover, the pathological approach has the singular advantage that "subclinical" manifestations of the disease become evident and can be evaluated. With few exceptions, reports based upon pathological findings of atherosclerosis show much smaller differences between races than those indicated by vital statistics and clinical data. Undoubtedly some of the sources of error inherent in vital statistics also influence necropsy statistics, so that reviews and summaries of autopsy records from different countries are not necessarily comparable. The finding of gross lesions in the coronary arteries of three-fourths of some

300 young American soldiers killed in Korea loses a little of its impact when similar lesions are found in 65% of a series of autopsies on Japanese natives (22), though the incidence of clinical coronary disease in Japan is said to be exceedingly low. Quite likely pathologists of many lands differ almost as much as do the clinicians in evaluation of their material. Particularly is this true of the quantitative estimates of severity of the disease. (Specifically, what constitutes a plaque? How many plaques, and how large, constitute significant disease? To what degree does the segmental distribution of lesions occlude a coronary artery? How general is "generalized arteriosclerosis" and how much, in a given case, did it contribute to morbidity or mortality?) Whether such judgments are to be in terms of the absolute degree of involvement or only of relative amounts, comparing one subject with another, some uniformity of criteria is essential for valid conclusions.

No system of grading of atheromatous lesions—short of a chemical analysis of lipid content, perhaps—can be completely objective. Plaques can be counted and measured as to size and degree of luminal occlusion, but an experienced pathologist's subjective impression on examining the specimen inevitably influences the grade assigned. Furthermore, the location of a lesion in the coronary arterial tree may be more important clinically than its severity. And the average degree of involvement of an artery may or may not denote the weakest link in the chain, the often sharply localized segment of greatest occlusion. Such sources of error are minimized when it is possible for one observer to examine pathological specimens without reference to their country of origin, race, age, sex, or other clinical data. Graded in this manner as to the severity of atheromatous disease, the hearts and aortas of Haitian and American Negroes, genetically similar groups living under radically different civi-

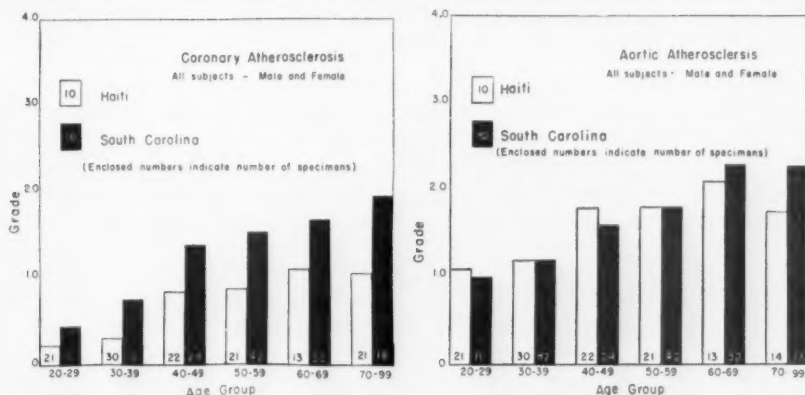


FIGURE 1. Average grades of coronary (left) and aortic (right) atherosclerosis of Haitian and American Negroes compared according to age decades. The striking disparity between the two populations in severity of coronary, but not aortic, manifestations of the disease was similar among both males and females.

lizations, yielded quite a different comparison than that implied by the vital statistics of the two countries. Hearts of the American subjects averaged almost double the degree of atherosclerosis and myocardial fibrosis (Figure 1), whereas no such difference was observed in the corresponding aortas (24). This held true for both males and females and at virtually all age levels over 20.

If the process of atheroma formation is fundamentally the same in both vessels (the fatty infiltration and degeneration of the intima, fibrous proliferation, ulceration, and calcification), and if this process is accelerated by the relatively high intake of cholesterol and fats in the American diet, one would expect the consequences in the aorta to parallel those in the coronary arterial tree. The reasons for the selective involvement of the coronaries are not known but they might well depend upon fundamental differences in function or structure between the aorta, which is regarded as a more or less passive elastic tube, and the coronary arteries, which are known to constrict actively in response to vasomotor and perhaps to humoral influences.

Variation in the localization of atheromatous disease seems to afford a promising lead. Almost nothing is known of why, for example, the Japanese should have a higher incidence of lesions involving the central nervous system and a lower incidence involving the coronary arteries than Americans, in whom the distribution is just the reverse (25, 26). A second look at some of the vital statistics from Africa discloses that, when the data are corrected for age-specific comparisons, the mortality rate from cerebral vascular disease among some of the Bantu groups is as high or higher than that of most white populations (27). Aortas of Jamaican Negroes are said to show a degree of atherosclerosis comparable to that found in the United States, yet only occasionally are these people known to succumb to ischemic heart disease (28). Thus it appears that, because of some factor or factors as yet unknown, *we grow old at different rates in the different vascular beds of the body.*

THE ROLES OF STRESS AND OTHER FACTORS

Certainly if the foods we eat are the chief cause for civilized white man's apparent predisposition to coronary disease we need

TABLE 2. Incidence of Various Factors in Young Coronary and Control Groups (29)

	No.	Heredity (Positive)	High-Fat Diet	Stress and Strain (Occupational)	Obesity	Tobacco (Excessive)	Exercise
Coronary group	100	67%	53%	91%	26%	70%	58%
Control group	100	40%	20%	20%	20%	35%	60%
Ratio		1.7:1	2.7:1	4.6:1	1.3:1	2:1	1:1

to revise our ideas of what constitutes a "normal" diet. But looking beyond the matter of diet, there are many obvious differences, of as great or greater magnitude, between a primitive existence where human muscles do much of the everyday work which in the United States has long since been relegated to machines and gadgets, where privation, infections, and deficiency diseases are the rule rather than the exception, education almost unknown, contrasted to the mechanization, complexity, tensions, and competitiveness of civilization as we know it. Fundamentally, the problem is one of what the entire environment of a race does to it as regards atherosclerosis. Unfortunately most of these imponderables are not measurable in precise units as are blood chemistries, but then neither are many other variables with which we deal daily in medicine under the category of "clinical judgment." One cannot ignore an observation simply because he cannot accurately measure or explain it.

Groups of patients with known coronary heart disease can be compared with ostensibly normal subjects concerning possible etiologic or predisposing influences in their heredity, diet, personality characteristics, etc., as depicted in Table 2. The implication is, at least in those groups who show manifestations of coronary disease early in life, that a stressful occupation may be a more potent determinant than heredity, diet, obesity, or tobacco, with physical exercise counting not at all. But whether stress can be estimated based on occupational status with any reliability is debatable. Stress is, after all, not so much one's

situation as his *reaction* to it. In a large-scale clinical study of executive and non-executive personnel followed over a five-year period no increased incidence of hypertensive or arteriosclerotic disease was observed in the executive class; actually there was a higher incidence of myocardial infarction among the nonexecutive group (30). Could it be that the successful leader learns better how to handle his tensions, to release them through outside avenues of expression such as hobbies? Does he perhaps encounter fewer frustrations along the way? Or is it simply a matter of natural selection whereby the healthier go higher?

Some degree of objectivity in appraising personality patterns may be achieved by the recording of various physiologic and motor phenomena, as in the popular "lie detection tests," which indicate graphically changes in response to emotionally charged stimuli. Under these circumstances supposedly distinctive responses can be obtained from patients with clinical coronary heart disease as contrasted to normal controls (31). Significant acceleration in blood clotting time and increases in serum cholesterol, both conceivably predisposing to thrombosis, have been described in the same patients in response to stress (32).

Physical exercise has its proponents, at the autopsy table as well as at the bedside. Table 3 is a compilation of data from several thousand unselected autopsies of the National Health Service in England (33) comparing reported pathology in coronary arteries with occupational status (physically "light" occupations being those of schoolmasters, bus drivers, clerks, and the

like, "active" those of postmasters, carpenters, etc., and "heavy" those of persons inured to strenuous work—the dock laborers, boilermakers, farm laborers, coal hewers). Considering the host of variables other than physical activity involved in such a classification by occupation, these figures are not very convincing. The age group 45 to 70 is a broad one, spanning most of the "coronary years"; if executives and others in sedentary occupations lived longer they would be expected to show more coronary disease. Furthermore, physical disability often influences one's choice of an occupation, and it is commonplace for men to seek jobs entailing limited physical exertion after they have experienced symptoms of coronary insufficiency. In spite of the scope of this investigation of autopsies numbering in the thousands, the results do not prove that the coronary arteries of men vary with the kind of work they do or,

indeed, with any other single factor of their environment. They do, however, bear out the need for more specific studies of a lead which has long intrigued clinicians.

A provocative and as yet virtually unexplored clue is that a negative correlation can be demonstrated between the hardness of water from public water supplies and the death rates from degenerative cardiovascular disease in the United States (34). States with high average values of hardness of their drinking water (and available reports show variations of more than 10 to 1 from state to state) have comparatively low reported death rates from coronary heart disease, while no such relationship holds for deaths from causes other than cardiovascular diseases. Certainly potable water is one variable to which all persons are exposed, and little is known of the physiological effects of many of the trace elements which contribute to the hardness of

TABLE 3. Coronary Artery Disease in Unselected Autopsy Material, Males Aged 45 to 70 (33), According to Physical Activity of Occupation

Coronary Artery Disease		"Basal" Group			"High" Coronary Artery Disease Group			All Noncoronary Deaths		
		Occupation			Occupation			Occupation		
		Light	Active	Heavy	Light	Active	Heavy	Light	Active	Heavy
	No. of cases:	995	1,034	668	445	395	194	1,440	1,429	862
(1) Coronary atherosclerosis present	Rate %	85	82	82	91	90	86	87	84	83
(2) Much coronary atherosclerosis with focal obstruction ("severe disease")	Rate %	10	9	10	24	17	22	14	11	13
(3) Much coronary atherosclerosis without focal obstruction	Rate %	5.7	6.0	4.6	9.3	8.4	9.0	6.7	6.6	5.7
(4) Calcification present	Rate %	19	18	18	32	26	31	23	20	21
(5) Focal obstruction present including (6)	Rate %	21	16	19	34	28	32	25	19	22
(6) Complete or near complete occlusion of a main coronary artery	Rate %	3.7	3.0	2.5	10.3	7.3	5.7	5.8*	4.2	3.2

* $0.02 > P > .01$.

water. If one accepts a causal relationship in these findings, it would appear that some factor, which is either present in hard water or missing in soft water, affects cardiovascular mortality selectively—that hard water protects, soft water predisposes.

Another etiological consideration which has attained popularity in recent years is that of the effects of tobacco on the cardiovascular system. Although the biologic actions of nicotine on heart rate, blood pressure, skin temperature, etc., have been recognized and measured for decades, only in recent years have the possible health hazards of smoking evoked more than casual or sporadic interest in medical circles. Sufficient data have been accumulated from mass surveys both in the United States and abroad to warrant a public statement by the American Heart Association that "death rates from coronary heart disease in middle-aged men were found to be 50 to 150% higher among heavy cigarette smokers than among those who do not smoke" (35). The conclusion is that excessive smoking "may contribute to or accelerate the development of coronary heart disease or its complications." Almost all the evidence cited in support of this conclusion has been derived from mortality and morbidity statistics of smoking and nonsmoking populations.

Obviously no single etiological factor elucidated thus far can explain all the observed facts of the atheromatous diseases. Nothing really fits, though a sort of composite man, caricatured in the footnote on the opening page, with a spotless heredity and the constitution of a euphoric ascetic, is beginning to emerge as the cardiovascular superman. Toward a more objective evaluation of these investigations, the following admonition bears repeating:

"A fundamental postulate for accurate inference from mass data is that the records which compose the data must be reasonably accurate and precise. Reasonably accurate and precise recording in turn demands that the observers agree on their definition of the phenomenon to

be observed and employ similar methods of reporting its occurrence. No amount of statistical skill can make up for the shortcomings of the original records of observations; the value of conclusions arrived at through statistical analysis is in direct proportion to the intrinsic value of the basic data. There is no magic in statistical methods. Bad statistics cannot be made good by mathematical formulae—a self-evident truism that is not always obeyed by the statistical methodologist nor realized by the non-statistical person whose faith in a set of figures is often too implicit" (36).

Significant population differences in incidence and severity of atherosclerosis do exist throughout the world—geographic, ethnic, perhaps occupational, cultural. It is too ambitious to aspire to a solution of civilization's number one health problem by population studies in the way the same epidemiological approach was utilized in the conquest of infectious diseases. Instinctively in medicine we look for a single cause. But the evidence is already overwhelming that atherosclerosis, like inflammation, is not due to any one cause and may not even be all one disease. Nevertheless from the wealth of epidemiological data—much of it conflicting, controversial, repetitive—come clues for the more definitive experiments of the laboratory.

The challenge is both one of improving the quality of our medical statistics and one of sifting from the morass of data those clues which are of real significance in the etiology of atherosclerosis. Apropos of the latter problem, common to many fields of endeavor, is Thomas Jefferson's hope that newspapers might someday classify their news under the headings *Facts*, *Probabilities*, *Possibilities*, and *Lies*.

But who can always be so discerning?

SUMMARY AND CONCLUSIONS

Studies of human populations have contributed impetus and unique insight to our understanding of atherosclerosis. They serve as nothing else can to delineate the natural history of the disease, often on a scale unprecedented in clinical medicine.

Most important, they deal with the end results in the human.

On the other hand, certain limitations inherent in this approach account for many of the conflicting interpretations and conclusions. Population studies are fraught with an appalling number of variables, with barriers of language, medical customs, and understanding which become greater as greater becomes the contrast in civilizations. They are of necessity uncontrolled and lack the precision of the planned animal experiment.

Vital statistics of the medically underprivileged country are not an accurate measure of the prevalence of atherosclerosis and cannot be weighed against those of a highly civilized people. Largely on the basis of such statistics, the concept has grown that the high fat diets associated with an economy of abundance cause high levels of lipids in the blood which, in turn, cause occlusive disease in the intima of arteries. Though evidence is overwhelming that fat metabolism is intimately related to atherogenesis, a second look at the population data shows strikingly similar correlations with environmental factors other than diet (stress, educational standards, competitiveness and drive, use of tobacco or telephones, trace elements in drinking water, occupation, and physical exercise) as well as with race, gender, family history, and perhaps aberrations of blood clotting.

Generally the more objective studies of pathologic material show lesser differences in incidence and severity of atheromatous disease. Moreover they disclose significant patterns of localization of lesions among populations (and individuals), the reasons for which are unknown. We grow old at different rates of speed in the different vascular beds of the body.

SUMMARIO IN INTERLINGUA

Studios demographic ha energisate e approfundate de maniera incomparabile nostre comprehension de atherosclerosis. Tal studios servi—como nihil altere pote facer lo—a delinear le

historia natural del morbo, frequentemente in dimensiones sin precedente in le medicina clinic. E illos se concerne—isto es le puncto le plus importante—con le resultados final in le homine.

Del altere latere, certe limitationes inherente in iste modo de investigation explica le confligente interpretationes e conclusiones. Studios demographic es incombrate de un astonante numero de variabiles, de barrieras de lingua, de costumes medical, e de conceptiones que cresce in tanto que cresce le differentias inter civilisationes. Iste variabiles es necessarimente sin normas de controllo, e le methodologia non ha le precision del planate experimentos animal.

Le statisticas vital que es disponibile pro medicalmente subdeveloppate paises non fornì un mesura accurate del prevalentia de atherosclerosis e non pote esser acceptate con le mesme peso como illos de altamente civilisate populos. Il es in grande mesura super le base de tal statisticas que le conception se ha establite que le dietas a alte contento de grassia (que es essociate con un economia de abundantia) es le causa de alte nivellos de lipidos in le sanguine le quales, de lor parte, produce morbo occlusive in le tunica intime del arterias. Ben que le indicios es fortissime secundo le quales il existe un intime relation inter le metabolismo de grassia e atherogenese, un plus critic re-examine del datos demographic revela frappantemente simile correlationes con factores de ambiente altere que le dieta (per exemplo stress, standard de education, rivalismo e ambition, uso de tabacco o telephones, elementos-tracia in le aqua potabile, occupation, exercitio physic, etc.) e etiam con racia, sexo, antecedentes familial, e forsan aberrationes del coagulation sanguinee.

A generalmente parlar, le plus objective studios de materiales pathologic monstra plus basse differentias de incidentia e de severitate del morbo atheromatose. In plus, illos revela significative mosaicos de distribution geographic del lesiones in varie populationes e de distribution anatomic de illos in varie individuos. Le rationes pro isto non es cognoscite. Nostre invetulation progredie con differente rapiditates in le diverse vasculaturas del corpore.

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The Effect of Estrogens on Atherosclerosis

A Post-mortem Study

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IN THE PAST much of the research concerning atherosclerosis has been directed toward prevention of the disease. Interest has been focused on particular groups, such as premenopausal women (1), Bantus (2), and Okinawans (3), who are relatively free of atherosclerosis presumably because of dietary habits or hormonal status.

Direct evidence of the effectiveness of estrogen has been provided by Pick, Stamler, Rodbard, and Katz (4), who were able by this means to inhibit development of coronary atherosclerosis in cholesterol-fed cockerels.

Of greater clinical importance is the question of whether atheromata, once it is present, can be resolved by therapeutic measures. In most clinical investigations of potentially useful therapeutic agents, because of the impossibility of direct observation of atheromata before and after treatment, alterations in plasma lipids have been used as the criteria of effectiveness. Barr, Russ, and Eder (5) showed that the administration of estrogen to middle-aged men "can affect the distribution of lipids in the plasma; the percentage of alpha-lipoproteins is increased, and the percent-

age in the form of beta-lipoproteins is correspondingly decreased." The final proportions approached those found in normal premenopausal women. Robinson, Higano, Cohen, Sniffen, and Sherer (6), and Barr et al. (5) demonstrated an increase in plasma phospholipids following estrogen therapy.

Several previous studies suggest more directly that atherosclerosis is reversible. Wilens (7) in 1947 demonstrated that marked weight loss a few months prior to death was associated with a profound reduction in atherosclerosis found at post-mortem. Rivin and Dimitroff (8) investigated the degree of atherosclerosis found at autopsy in men with carcinoma of the prostate who had been treated with estrogens. Their studies showed fewer lesions of coronary atherosclerosis among a group of men treated with 75 mg of diethylstilbestrol a day than among a control group, but a smaller group who received 15 mg or less of diethylstilbestrol per day showed no difference from the controls. No effect upon aortic or cerebral atherosclerosis was demonstrated (6).

In the present study, the arteries of a group of men treated with estrogens for carcinoma of the prostate have been compared post-mortem with those of a control group with prostatic cancer who received no hormonal therapy. The dosage of estrogen was substantially lower than in relevant previous reports. The findings suggest that this therapy significantly reduced the severity of atheromatous lesions. Their implication for the potential reversibility of such lesions is discussed.

Received for publication November 18, 1960.

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Aided by a grant from the John A. Hartford Foundation, Inc.

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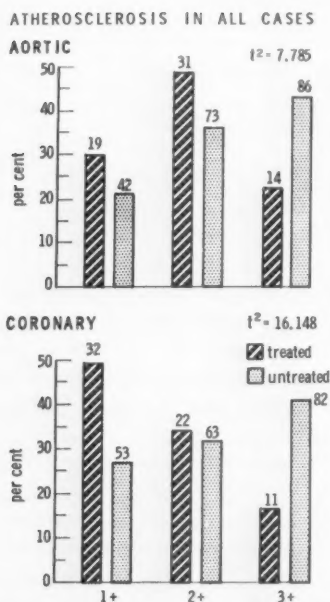


FIGURE 1. Distribution of severity of aortic and coronary atherosclerosis among all estrogen-treated and all untreated cases. (In this and subsequent bar graphs, the number at the head of or within each column indicates the number of cases studied.)

MATERIALS AND METHODS

For this study, the protocols were reviewed of all cases of carcinoma of the prostate examined at autopsy at Bellevue Hospital, New York Hospital, Queens General Hospital, and Memorial Hospital between the years 1947 and 1957.

The degree of atherosclerosis, as described by the prosector, was graded as 1+ (absent or mild), 2+ (moderate), or 3+ (marked or severe), following the criteria of Wilens (7, 9, 10). These evaluations were done without prior knowledge of whether the patients had been treated with estrogens. Where the prosector's description was considered inadequate the case was excluded from the study, with the grader still unaware of whether the patient had received estrogen.

The age of the patient, the state of nutrition, as represented by thickness of the

panniculus, and evidence of surgical castration were noted and incorporated into the final evaluation of the data. Information regarding weight loss prior to death was not available.

After all grading was done, the clinical records were consulted. In the treated group were included all cases receiving estrogens, usually diethylstilbestrol, for three or more months, regardless of the dosage. The limit of three months was selected because this is approximately the minimal time required to obtain objective evidence of estrogen effect, such as gynecomastia (8). The dosage of estrogens varied slightly, as did the preparation used, but the majority of the treated cases received diethylstilbestrol in doses of 5 to 15 mg daily, or equivalent doses of other agents. This dosage level was recommended by most urologists

ATHEROSCLEROSIS: CASES WITH EXTRA FACTORS REMOVED

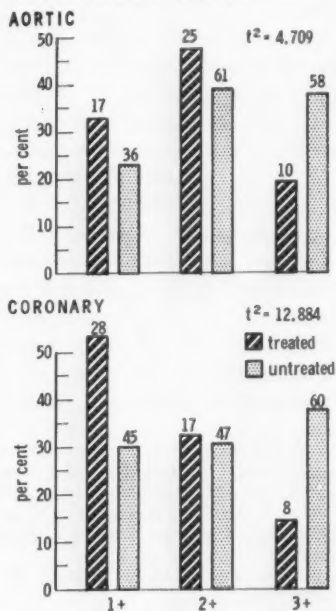


FIGURE 2. Comparison of treated and untreated groups after elimination of cases having evidence of diabetes, hypertension, or valvular heart disease.

in this area during the period of this study (11).

While cases of occult carcinoma of the prostate, confined to the gland and evident only on microscopic examination of post-mortem sections, were uniformly excluded, the extent of the neoplastic process found at autopsy varied widely both in the treated and untreated groups. In only a small minority of cases was death considered due to cachexia resulting from carcinomatosis.

RESULTS

The estimated severity of atheromatous lesions in the aortas and coronary arteries of the entire series of 265 cases is presented in Figure 1. It is evident that the distribution of degree of atherosclerosis has been altered by estrogen therapy. Using the rank t test for statistical significance (12), the t^2 value for the aortas is 7.785 and for the coronary arteries is 16.148. Both are significant at the 1% level.

In Figure 2 are shown the findings for the balance of the series, after excluding all patients with clinical histories of diabetes or of hypertension, as well as all

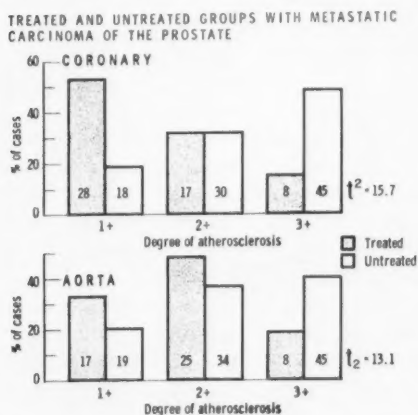


FIGURE 3. Comparison of treated and untreated groups after exclusion of all cases with extraneous cardiovascular and metabolic factors and all cases dying without metastases.

EFFECT OF AGE ON ATHEROSCLEROSIS

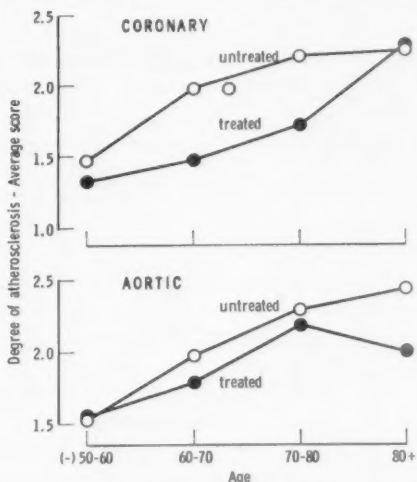


FIGURE 4. Effect of age on severity of atherosclerosis in the present series (see text).

patients with post-mortem findings of lesions of the heart valves or hearts that weighed over 425 grams. This was done to eliminate extraneous factors which might have influenced the severity of atherosclerosis (9, 10). The cases with grossly enlarged hearts were removed from consideration because in the absence of valvular lesions this finding can usually be considered evidence of hypertension (10). It may be noted in passing that almost all the diabetics, whether or not they were treated with estrogen, manifested a severe degree of atherosclerosis.

Figure 2 illustrates the difference between the treated and untreated groups with these cases removed. The t^2 values have decreased somewhat, but still indicate differences in coronary atherosclerosis which are significant at the 1% level, and in aortic atherosclerosis at the 5% level.

Because the treated group differs from the untreated group in that it contains only cases with metastatic carcinoma of the prostate, a further comparison is made (Figure 3) in which all untreated cases

EFFECT OF NUTRITION ON ATHEROSCLEROSIS

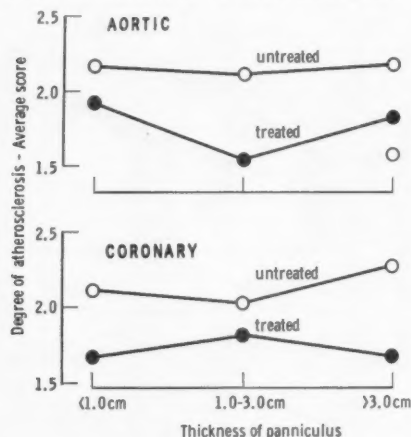


FIGURE 5. Lack of relationship in the present series between state of nutrition (indicated by thickness of abdominal panniculus) and degree of atherosclerosis.

without metastases have been excluded. The t^2 values are now seen to be greater than in the previous comparison, and the differences for both aortas and coronary arteries are significant at the 1% level.

Since age is believed to affect atherogenesis, this factor is taken into account in Figure 4, where the degree of atherosclerosis is plotted against the age, in decades, of the patients at time of death. As the bulk of the cases were 60 to 80 years of age, less significance can be attached to the scores for the youngest and the oldest groups. The average ages of the entire treated and untreated groups differed by only a half-year. Though atherosclerosis increases with age, this is not the cause of the difference between the treated and the control groups.

The factor of nutrition is considered in Figure 5. Thickness of the abdominal panniculus in centimeters is plotted against average degree of atherosclerosis. In this series the general level of nutrition per se did not seem to affect atherogenesis. The great majority of these patients, as do most

patients with advanced carcinoma, fall into the moderately to poorly nourished groups, with a panniculus less than 3 cm thick. It would appear from the graph that the study was not biased by nutritional factors, and that at each level of nutrition atherosclerosis is less severe in the treated group.

The influence of duration of treatment on the effect of estrogens on atherosclerosis was next considered. In Figure 6 the average scores, using the 1+ to 3+ scale, were determined for all cases falling within each indicated time interval. The cases with extraneous cardiovascular factors were not included. The first point on each curve represents the average score of the entire untreated control group (zero to three months of estrogen therapy). This first point, representing over 200 cases, is thus more significant than each of the succeeding points, which represents the average of 10 to 15 cases. The curves are irregular, but it would appear that at least six to 12

EFFECT OF DURATION OF THERAPY ON ATHEROSCLEROSIS AND NUTRITION

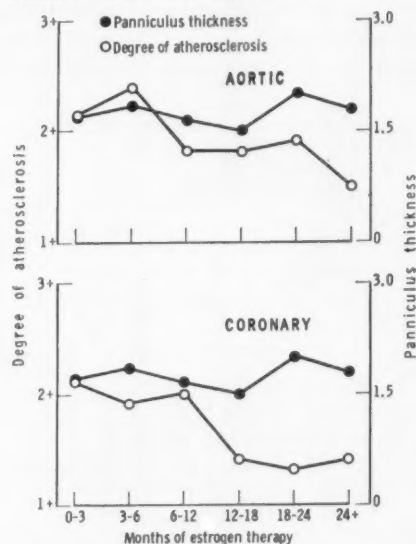


FIGURE 6. Prolongation of therapy with estrogen causes reduction in average degree of atherosclerosis but no changes in thickness of panniculus.

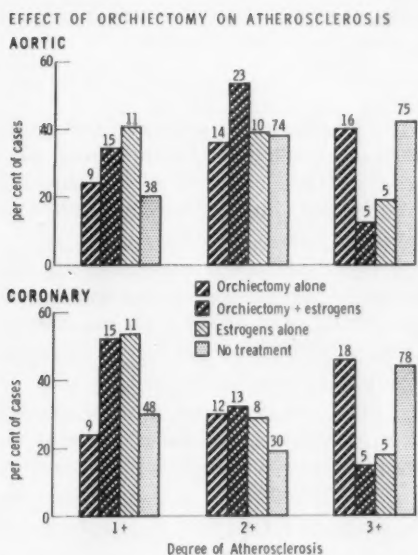


FIGURE 7. Effect of orchiectomy, with and without use of estrogens, on severity of atherosclerosis.

months of estrogen therapy with 5 to 15 mg of stilbestrol daily is necessary to produce significant improvement in coronary and aortic atherosclerosis. The amelioration noted with therapy of longer duration is not a consequence of progressive emaciation. There is no significant change in nutrition, as measured by average thickness of the panniculus, at any point on these two curves.

The effect of orchiectomy upon coronary and aortic atherosclerosis was next considered (Figure 7). In general, the distribution of severity of atherosclerosis among those patients who had orchiectomy alone (column 1, each group) is approximately the same as among those who received no therapy (column 4). Orchiectomy plus estrogen therapy (column 2) did not cause greater improvement than estrogens alone (column 3).

DISCUSSION

The conclusions to be drawn are limited by the fact that this is a retrospective study.

The investigators were not able to examine directly the blood vessels evaluated, but had to rely on the prosector's description in the autopsy protocol. To compensate for this, bias was eliminated insofar as possible through blind grading, and the grading scale employed defined only very gross differences in severity of atherosclerosis. Three degrees were recognized, a grouping previously used and found feasible by Wilens (7, 9, 10). Cases having other cardiovascular and metabolic disorders, which are known to influence the degree of atherosclerosis, were eliminated. The factors of age and nutrition were considered separately and found not to be critical.

The differences observed might be explained by considerations affecting the decision whether to treat with estrogens in each case. Thus, patients who appeared not to be severely affected by their carcinoma (and therefore likely to remain in a good state of nutrition) and to be subject to normal environmental stresses, would more often be left untreated. The treated and untreated groups did differ in that the former included only cases with metastatic disease, while in some of the latter the tumor had not metastasized. When untreated cases without metastases are excluded from consideration, however, the differences could be discerned in the average extent of metastatic disease found at autopsy between the remaining untreated cases and the treated cases. Furthermore, the average level of nutrition for the untreated group, as measured by thickness of the panniculus, does not differ from that of the treated cases, whatever the duration of therapy.

The assumption can be made that prior to therapy the distribution of severity of atherosclerosis among the treated and untreated groups was approximately the same. Since the period of treatment in each case was quite short when compared to the patient's life span, the differences observed between the treated and control groups

must result from actual removal of atheromatous material from the intima of the arteries, rather than representing mere arrest of the disease process. This would indicate that atheromata are not "fossils" but are metabolically active deposits, the formation and the resorption of which can be altered by therapeutic agents.

From this study it would appear that reversal of atheromatous lesions can be obtained with diethylstilbestrol in doses of 15 mg per day (or equivalent amounts of other estrogens) if the therapy is continued for six months to one year. This contrasts with the findings of Rivin and Dimitroff (8), who were able to demonstrate a therapeutic effect only at a dosage of 75 mg per day. The greater effectiveness of estrogenic therapy on lesions of coronary arteries than on those of the aorta has been noted previously in men (8) and in chicks (4). Orchiectomy alone did not alter the severity of atherosclerosis, nor did orchiectomy potentiate the effect of estrogen therapy. Therefore, either the testicular hormone output of patients in the older age group is so low as to have little effect upon atherosclerosis, or the critical factor is not the level of *androgen* but the level of *estrogen*.

The data presented here appear to confirm the earlier indications by Wilens (7) and by Rivin and Dimitroff (8) that atherosclerosis in man may be a reversible process. It seems possible to reduce the degree of atherosclerosis by dosage schedules of estrogenic therapy already shown, in experience with patients having carcinoma of the prostate, to be without dangerous effects, using in some instances actually less than the doses found by Barr and others (5, 13) and Robinson et al. (6) to alter plasma lipid patterns. Yet, because even these doses are associated with profoundly disturbing symptoms and feminizing effects, estrogens are far from being ideal therapeutic agents. It is hoped that in the future other therapeutic measures, known to have similar effects on plasma lipids, will be evaluated

directly for their effects on the severity of atheromatous lesions in man.

SUMMARY

1. The degrees of coronary and aortic atherosclerosis found at autopsy were compared in two groups of men with carcinoma of the prostate, one untreated and the other treated with estrogens.

2. Significantly less atherosclerosis was found in the estrogen-treated group, but the severity of coronary lesions seemed to be more profoundly affected by estrogens than was the severity of aortic lesions.

3. Orchiectomy did not affect the degree of atherosclerosis, nor did it augment the effect of estrogen therapy.

4. The implications of these findings for the potential reversibility of atherosclerotic lesions are discussed.

ACKNOWLEDGMENTS

We acknowledge with gratitude the cooperation of Doctors Marvin Kushner, Frank W. Foote, John T. Ellis, and Herman Steinberg, and the statistical consultation provided by Irvin D. J. Bross, Ph.D.

SUMMARIO IN INTERLINGUA

Per le utilisation del methodos de pathologia experimental e a base de studios del prevalentia de atherosclerosis in varie populationes human, il esseva trovate que varie factores affice le formation de atheroma. Tamen, le influentia de iste factores in jam establite lesiones atheromatose non es ben cognoscite. Viste le facto que le administration de estrogenos a masculos de medie etates se ha provate capace de alterar le distribution de lipidos e lipoproteinas del plasma verso le configuration trovate in normal feminas premenopausal, nos ha tentate trovar provas de un effecto de prolongate cursos de therapia estrogenic super le severitate de pre-existente atherosclerosis.

Nos ha scrutinate le protocollos de omne le casos de carcinoma del prostata examinate post morte a quatro hospitales inter le annos 1947 e 1957. Le reportate grado de atherosclerosis del arterias coronari e del aorta esseva qualificate in omne caso individual como leve, moderate, a sever. Postea le casos esseva subdividite in duo gruppos: (1) Le gruppo con tractamento,

consistente de 65 casos recipiente 5 a 15 mg per die de diethylstilbestrol (o altere estrogenos in un dosage equivalente) durante 3 menses o plus, e (2) le gruppo sin tractamento, consistente de 201 casos recipiente nulle therapia estrogenic o un dosage de illo inferior al valores usate in le prime gruppo.

Tanto in le arterias coronari como etiam in le aortas, le severitate del lesiones atherosclerotic esseva plus basse (al nivello de 1% de signification) in le tractate que in le non tractate gruppo. Iste constatacion non pote esser attribuite a differentias de etate, a obesitate, o al presentia associate de diabete o hypertension. Le reducite severitate de atherosclerosis es apparente solmente in le casos in que le tractamento habeva durate sex a 12 menses o plus. Orchiectomy bilateral, que habeva essite effectuate in 66 del casos, exerceva nulle effecto benefic.

Si nos suppone que le duo gruppas habeva al comenciamiento del therapia nulle significativa differentia in le severitate medie de lor atherosclerose, le resultados del studio debe indicar le reversion del establite lesiones durante le administration de estrogeno.

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Primary Hyperoxaluria

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PRIMARY HYPEROXALURIA IS CHARACTERIZED by an increased urinary excretion of oxalate and the deposition of calcium oxalate crystals in the kidneys and other organs. This metabolic defect was thought initially to be a severe disease of infancy and childhood, characterized by recurrent nephrolithiasis and pyelonephritis and by a progressive course terminating in a uremic death. Studies by Newns and Black (1) in 1953 and by Aponte and Fetter (2) in 1954 demonstrated an increased urinary excretion of oxalate prior to death in such patients. Subsequently, the disease has been diagnosed with increasing frequency during life, and others (3-7) have confirmed the relationship of "hyperoxaluria" during life to "oxalosis" on necropsy study. Wider use of urinary oxalate determinations and the increased interest in hyperoxaluria has led to the recognition and recent reporting of many cases (4, 6, 8, 9-13) since the known cases were summarized in 1957 (14), 1958 (15), and 1960 (7); with the patients reported herein, the total number of cases of hyperoxaluria-oxalosis known to us is 53.

Although the exact nature of the underlying metabolic defect in primary hyperoxaluria has not been uncovered, the recognition of this disease during life now makes it possible to conduct studies with

the hope of defining or localizing the enzymatic defect which apparently is present in these patients. Metabolic studies (9, 15, 16) and radioisotopic studies (12, 17, 18) have been reported from several centers, and there is a growing fund of knowledge concerning the metabolic pathways of various precursors (9, 12, 15, 17-21) which contribute to the endogenous formation of oxalate.

It is the purpose of this report to characterize the clinical picture of the milder forms of primary hyperoxaluria as seen in four patients. In addition, studies attempting to influence oxalate excretion with pyridoxine, glycine, benzoate, and ascorbic acid in patients and in a control subject will be discussed.

CASE REPORTS

CASE 1

A ten-year-old white male passed his first renal calculus at 21 months of age. Subsequently, other stones were passed spontaneously during his fourth, fifth, and sixth year, and ureterolithotomies were required at two and one-half and seven years of age. At the age of six, his neck was explored and four parathyroid glands were identified, none of which was enlarged. Nephrolithiasis was not present in any known relative.

Physical Examination: Routine urinalysis, hemogram, and serum electrolytes were within normal limits at this hospital in 1959. There was no nitrogen retention or any biochemical abnormality suggestive of hyperparathyroidism. Urine cultures were consistently positive for *Aerobacter areogenes*. An excretory urogram re-

Received for publication February 20, 1961.

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vealed multiple bilateral renal stones which measured 1 to 22 mm in diameter. The diagnosis of hyperoxaluria was established when the patient's urinary oxalate excretion was found to range from 190 to 290 mg per day.

The patient was treated with 50 mg per day of oral pyridoxine and antibiotics to control the urinary tract infection. He has been asymptomatic during the ensuing 12 months. Twenty-four-hour urine collections showed an oxalate content of 420 mg and 360 mg, respectively, after six and nine months on pyridoxine.

Comment: This patient resembles other reported cases of oxaluria with regard to onset in early childhood and repeated episodes of renal colic. However, to date he has no stigmata of the characteristic progressive renal failure or hypertension.

CASE 2

The illness of a 51-year-old white housewife began at 16 years of age with passage of a renal calculus. Since that time she has passed stones spontaneously at least once a year. Ureteral lithotomies were necessary in 1935, 1947, and 1958. Chemical analyses of several stones have revealed them to be composed of calcium oxalate.

Repeated evaluations for hyperparathyroidism have been negative. She has had six episodes of paroxysmal atrial tachycardia since 1946, and is maintained on digitalis and quinidine. Her only pregnancy resulted in a full-term stillborn infant. Family and past medical history were not remarkable. Physical examination was within normal limits. Routine laboratory studies at this hospital, including urinalysis, hemogram, blood urea nitrogen, and serum electrolytes, were normal. Urine cultures showed no growth. Renal function studies showed a glomerular filtration rate (inulin clearance) of 86 ml per minute and an effective renal plasma flow (PAH clearance) of 551 ml per minute. Electrocardiograms showed non-specific ST-T wave changes compatible with digitalis effect and/or myocardial ischemia.

After the diagnosis of hyperoxaluria had been established by the consistent elevation of urinary oxalate excretion of 200 to 654 mg per day, the patient underwent the metabolic balance study to be described subsequently. Thereafter, she was treated with oral pyri-

doxine in a dosage of 50 mg per day. She has been asymptomatic for 18 months on this therapy, and urinary oxalate excretions after six and nine months were 224 and 125 mg per day, respectively.

Comment: This patient is atypical of the early reported cases of primary hyperoxaluria because of her relatively late onset of symptoms (age 16), absence of hypertension, and prolonged survival. Although she has depression of glomerular filtration and renal plasma flow after 37 years of stone formation, she remains free of uremia. It is interesting to speculate that her repeated episodes of cardiac arrhythmia might be triggered by oxalate crystal formation in the myocardium (6).

CASE 3

A 26-year-old white female first passed renal calculi in infancy. On three subsequent occasions she had right costovertebral angle pain which was thought to be due to a renal calculus. Excretory and retrograde urograms have not demonstrated specific renal pathology. In 1959, the patient delivered a viable, full-term infant without complications following a benign prenatal course. Gout was suspected in 1953 because of an acute transient arthropathy involving the right great toe, but it could not be confirmed. Infectious mononucleosis was diagnosed in 1956. The patient's mother and maternal grandmother have passed renal stones, but no other member of the family is known to have nephrolithiasis.

Physical examination and laboratory studies were within normal limits except for an excretion of 245 mg of oxalate in 24 hours. All urine cultures have contained a species of *Proteus*, but urinalysis was otherwise normal.

Comment: This patient had the typical early onset of urolithiasis and three subsequent episodes attributed to calculi. However, the lack of radio-opaque renal calculi is unusual, as oxalate stones are roentgeno-

graphically quite dense. Family history is suggestive of a dominant inheritance, which is different from most reported experiences except for one instance (9, 11). Unfortunately, confirmation of the family history with urinary oxalate measurements has not been possible.

CASE 4

A 36-year-old white female passed a calculus from the left ureter in 1955. Immediately following this episode she passed small amounts of "gravel" without difficulty. She was asymptomatic until 1959, at which time she had a recurrence of colicky left flank pain, and passed a calculus. Physical examination was within normal limits. Family history revealed that her mother and younger sister have had urolithiasis. Excretory urograms showed small bilateral renal calculi. A thorough evaluation for the known causes of urolithiasis was negative in 1959 except for excretion of 72 mg of oxalate per 24 hours and urine cultures which contained *Escherichia coli*.

Comment: This patient is atypical of reported cases because of the late onset of the disease and infrequent episodes of urolithiasis without evidence of renal failure or hypertension.

METABOLIC STUDIES

ROUTINE STUDIES

Clinical laboratory studies included complete blood counts, urinalyses, and urine cultures. Determinations of blood urea nitrogen, serum creatinine, uric acid, glucose, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, total protein, serum albumin, and alkaline phosphatase were carried out as standard clinical laboratory procedures. The results obtained are listed with each case, or were within normal limits. Urinary oxalate was determined following the method described by Archer, Dormer, Scowen, and Watts (22, 23). The values obtained by us in 31 normal individuals ranged up to 63 mg per day of

urinary oxalate excretion. The mean and one standard deviation was 28.2 ± 17.5 mg per 24 hours, which is in close agreement with values for normal oxalate excretion as published by others (12, 19, 20, 22, 23).

SPECIAL STUDIES

A paired metabolic study was conducted on Case 2 and a 25-year-old healthy white male control subject. A solid diet was employed which contained 1 g/kg of protein and 35 cal/kg each day. Twenty-four-hour urinary specimens were collected on a metabolic balance ward and were monitored by creatinine determinations. Control periods were alternated with test periods in blocks of three days each. The individual effects on urinary oxalate excretion of 20 g per day of oral sodium benzoate, 4 g per day of ascorbic acid, 20 g per day of glycine, and 100 mg per day of pyridoxine were evaluated.

Benzoate administration was studied because of the possibility that it would combine with glycine to form hippuric acid and thereby deplete the "pool" of glycine available for degradation to oxalate (15). Glycine, shown to be a precursor of urinary oxalate by isotopic methods (12, 17, 18), was administered in an attempt to see if quantitative increases in urinary oxalate would accompany large oral doses of glycine. Ascorbic acid has also been shown by isotopic methods to be a precursor of urinary oxalate (21, 24), and large oral doses have been shown to increase urinary oxalate excretion (20). The attempt to lower urinary oxalate levels with oral pyridoxine was based on observations in animals (25, 26) that pyridoxine-deficient diets were accompanied by calcium oxalate nephrolithiasis and by observations that pyridoxine administration in man was associated with a fall in urinary oxalate excretion (16).

The results of these studies are shown in Figure 1. With the possible exception of a slight reduction of urinary oxalate excre-

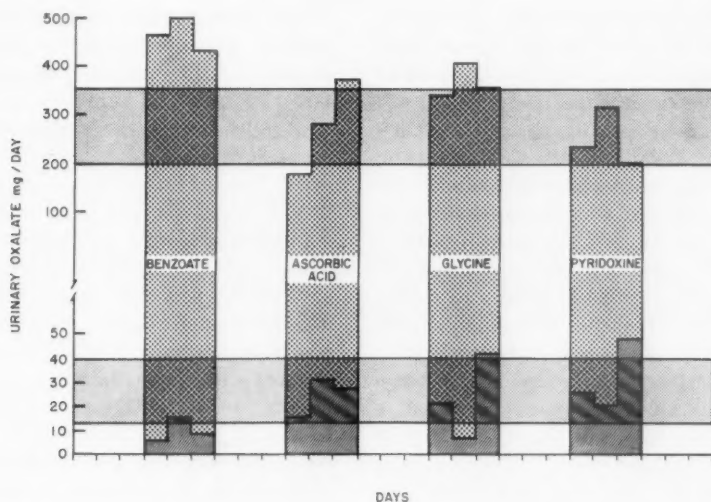


FIGURE 1. The comparative responses of urinary oxalate excretion to various agents. Three-day periods of oral administration of these drugs were separated by three-day control periods, as shown. A hyperoxaluric patient (upper scale) is compared to a normal subject (lower scale). The horizontal bars represent the mean ± 1 SD of all control days.

tion associated in the normal control subject with benzoate administration, the various attempted manipulations failed to influence oxalate excretion in the patient or in the normal control. In both subjects, the day-to-day fluctuation in oxalate excretion during control days was relatively large despite the controlled diet.

LONG-TERM PYRIDOXINE THERAPY

Despite the failure of short-term pyridoxine therapy to induce a fall in urinary oxalate excretion in Case 2, a trial of long-term therapy was attempted. Accordingly, Case 1 was given 50 mg of pyridoxine daily for 12 months. His excretion of oxalate was 420 mg per 24 hours at six months and 360 mg per 24 hours at nine months after treatment. Case 2 was given 100 mg of pyridoxine daily for 18 months. Her excretion of oxalate was 224 mg per 24 hours at six months and 127 mg per 24 hours at nine months after treatment. Urinary oxalate excretion remained unchanged in these

patients. While no definitive conclusions can be drawn from these data, neither patient has had symptoms of nephrolithiasis since the institution of therapy.

DISCUSSION

PRIMARY HYPEROXALURIA

The increasing use of quantitative urinary oxalate measurements has led to the realization that the syndrome of hyperoxaluria includes a broad clinical spectrum. This ranges from the asymptomatic adult to the infant dying of renal failure. For unknown reasons, the major organ of oxalate deposition is the kidney. Nephrolithiasis, hematuria, or pyelonephritis is the most typical presenting finding in hyperoxaluria; in the milder variants, these may not occur until adolescence or early adult life, and may be the sole manifestations of disease. Progressive destruction of kidney tissue is most likely to be the combined result of a continuing oxalate deposition and superimposed pyelonephritis.

The presence of hyperoxaluria per se does not appear to interfere with normal patterns of growth or development unless renal failure supervenes.

Pathologic findings in patients with hyperoxaluria (3-5, 7, 10, 14, 27-31) comprise a pattern which correlates closely with the clinical course. In addition to deposits in the kidneys, deposits in bones, myocardium, muscles, and connective tissues are less common sites of occurrence. Deposits also occur in the media of smaller arteries and arterioles, and in these locations have been reported widely throughout the body. In addition to renal lesions and oxalate deposits, uremia contributes its typical pathologic changes.

While primary hyperparathyroidism has been eliminated as a cause of hyperoxaluria, secondary hyperparathyroidism has been seen (27-29, 32). Necrotic renal tissue from any cause may be the site of a secondary deposition of calcium oxalate (33).

Primary hyperoxaluria must be differentiated from renal tubular acidosis. Simko (32) has reported detailed renal function studies which demonstrate poor ammonia synthesis, poor acidogenesis, and poor reabsorption of bicarbonate in a child with hyperoxaluria. Similarly, Dunn (29) described decreased ammonia synthesis in his case, and DeToni, Durand, and Rosso (34) reported the findings of hyperchloremic renal acidosis with severely impaired ammonia genesis in a patient with hyperoxaluria. These derangements denote functional alterations of the distal renal tubule and resemble the biochemical patterns observed in patients with renal tubular acidosis. While Simko has suggested that oxalate deposition may be secondary to a primary distal tubular defect, review of the reported cases makes it seem more likely that oxalate deposition and destruction of renal parenchyma are primary. In this respect, it is of note that Kempsey, Forbes, Melick, and Henneman (19) men-

tioned three patients with "renal tubular acidosis" who showed slightly elevated excretions of urinary oxalate, and four others who had a normal urinary oxalate excretion (as did one patient with renal tubular acidosis observed by us).

SECONDARY HYPEROXALURIA

In contrast to the patients in whom increased urinary oxalate excretion appears to be a primary metabolic defect, elevations of urinary oxalate have been reported which are apparently secondary to, or associated with, high dietary intakes of oxalate or protein, diabetes, cirrhosis, cardiac failure, nutritional disturbances, sarcoidosis, or intestinal parasites (35). Ethylene glycol poisoning also gives rise to secondary hyperoxaluria (36). Based on the evidence that dietary deficiencies of magnesium, vitamin A, and vitamin D (37) or of pyridoxine (16, 25, 26) in animals is associated with hyperoxaluria and oxalate stone production, it appears possible that many of the above-listed causes for secondary oxaluria might be related to a poor nutritional state, avitaminosis, or impaired hepatic function. Perhaps the marked, transient rise in the incidence of oxalate stone formation in Central Europe during and after World War I was due to this kind of dietary deficiency (35, 38).

DIAGNOSTIC CRITERIA

Primary hyperoxaluria should be suspected as a possible diagnosis in any patient with nephrolithiasis, nephrocalcinosis, or recurring pyelonephritis. Screening studies of such patients should include 24-hour determinations of urinary oxalate levels. Because of the observed day-to-day variability, patients who show excretion values which approach the upper limits of normal should be rechecked by at least three 24-hour determinations. The significance of borderline elevations of oxalate excretion is yet unclear; some relatives of patients with hyperoxaluria mentioned by Scowen,

Watts, and Hall (11) have shown borderline oxalate elevations without clinical evidence of disease. The various primary conditions which may be associated with hyperoxaluria, as listed above, should be ruled out. The fact that several urine specimens of our nonuremic patients with hyperoxaluria showed oxalate values higher than any previously reported supports the view that renal failure may lower the high oxalate excretion of this disease (6). Post-mortem elevation of spinal fluid oxalate has been reported (5) but not confirmed in the living patient.

HEREDITARY ASPECTS

The recognition of primary hyperoxaluria during life has stimulated the search for the genetic background of this apparently hereditary condition. On the basis of a study of 13 cases from eight families (11) and the majority of other families reported in the literature, recessive inheritance seems to be the most common. However, the study reported by Shepard, Creighton, Krebs, Lee, and Thuline (7) and the family histories obtained in Cases 3 and 4 of our series suggest that a dominant inheritance is also possible. The earlier reported cases of oxaluria showed a predominance in males, but with additional studies no sex difference seems apparent. Further information is necessary to delineate the hereditary patterns involved in hyperoxaluria and to determine if the observed variations in severity of the disease are due to difference in penetrance.

THERAPY

There has been no noticeable clinical success in various methods attempted to control hyperoxaluria by decreasing oxalate absorption (2, 27, 39). These have included low oxalate diets or the use of milk to lower the solubility of oxalate in the gut. Diets low in oxalate, glycine, or protein have shown relatively little success in lowering urinary oxalate in patients

(15), nor has benzoate therapy offered much hope of success. Citrate administration has failed to halt the progress of the disease (28) but has improved the clinical status of a patient with renal insufficiency and hyperchloremic acidosis (33). Balanced diets with a vitamin content high in A and D have been recommended (29, 35). Magnesium therapy has been suggested (35, 37) but no apparent success occurred in a trial in a patient with this disease (4). The use of oral pyridoxine therapy remains an unproven possibility which is worth pursuing.

With our present inability to lower the oxalate excretion in patients with primary hyperoxaluria, the primary aim of therapy should be directed toward a meticulous control of superimposed urinary tract infections and the correction of any mechanical problems produced by oxalate deposition. If renal failure supervenes, usual therapeutic measures should be employed in an effort to maintain normal electrolyte homeostasis and to minimize the degree of uremia.

OXALATE METABOLISM

In a classic review of oxalate metabolism, Jeghers and Murphy (35) pointed out that the recognition of calcium oxalate crystals in the urine in the early nineteenth century was followed by descriptions of numerous syndromes such as oxaluria, oxalemia, oxalic acid diathesis, and oxalic gout. Since these included various neuroathenic or rheumatic symptoms in association with the presence of oxalate crystals in the urine, they eventually became diagnostic "scrap baskets" and were largely discarded from clinical thinking. Research in oxalate metabolism has been hampered by the lack of reliable methods to measure oxalate in the blood and by the infrequent use of quantitative urine measurements. The wider employment of urinary oxalate determinations and the use of radioisotope

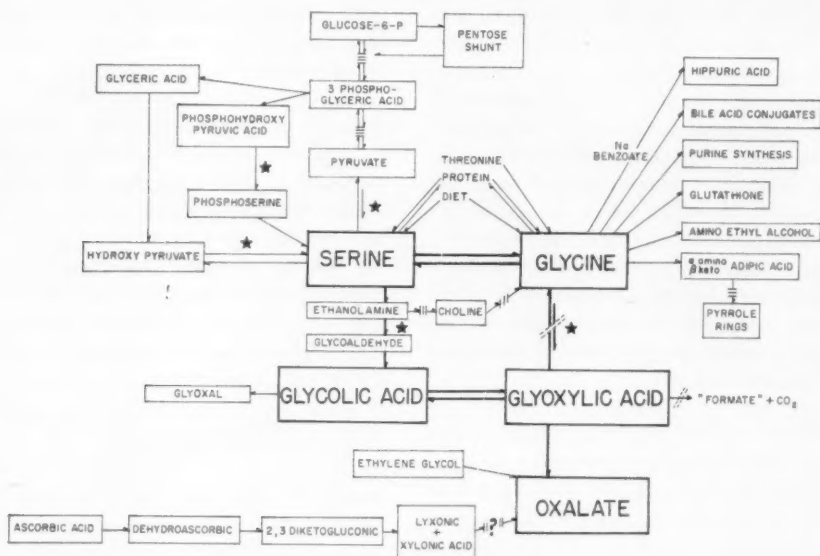


FIGURE 2. Metabolic pathways leading to oxalate formation. Transamination reactions are indicated by a small star and indicate sites where vitamin B₆ may be required as a cofactor. A possible block may exist in hyperoxaluria between glyoxylic acid and glycine; since degradation of glyoxylic acid to "formate" and CO₂ has not been demonstrated except in bacteria, there seems to be little chance that such a reaction is involved in hyperoxaluria.

techniques has led to the recent upsurge in interest in oxalate metabolism.

Oxalate is an end product of metabolism in the human (12). Our concept of the metabolic pathways leading to oxalate formation is presented in Figure 2 and is based on known pathways of intermediary metabolism in man or suspected on the basis of studies reported in both humans and animals. As depicted, a cycle involving glycine, serine, ethanolamine, glycolic acid, and glyoxylic acid seems to exist, with oxalic acid being derived from glyoxylic acid as a metabolic end-product. Isotope methods have been helpful in delineating the metabolic pathways leading to oxalate formation in both humans and animals. Early studies of the metabolism of two carbon compounds (40) showed that oxalate is metabolically inert and that both glycolic and glyoxylic acid are converted to oxalate as well as to glycine. In later stud-

ies, Friedman, Levin, and Weinhouse (41), showed that glycoaldehyde was also converted to glycine with smaller amounts appearing as oxalic acid. Using glycine-1-C¹⁴ in normal and hyperoxaluric human subjects, it was found that 40% of the urinary oxalate comes from the glycine pool in normal humans (18). Fifty per cent and 32% of urinary oxalate was derived from this pool in two patients with primary hyperoxaluria (17). Elder and Wyngaarden have performed similar studies using carbon-tagged glycine in six normal patients (12). They showed that the urinary oxalate was labeled rapidly after the administration of glycine in control subjects, with a subsequent loss of oxalate radioactivity in approximately 24 hours. A patient with hyperoxaluria showed incorporation of radioactivity into urinary oxalate four times greater than did the control subjects. Although glycine is a major precursor of

urinary oxalate, an appreciable percentage must come from other sources.

Source of Urinary Oxalate: Oxalate excreted from the body has been thought to come from the oxalate content of food, from oxalate produced by intestinal bacteria, and from the products of intermediary metabolism within the body. More recent studies make it appear that a large percentage of urinary oxalate is derived from endogenous sources (12, 17, 18). Archer and his co-workers (15) administered increasing amounts of oxalate to normal individuals and showed that only 2.3 to 4.5% of the dose appeared in the urine. Conversely, the failure to influence significantly the excretion of urinary oxalate in patients with hyperoxaluria by lowering the dietary oxalate content has been recognized (2, 27, 29), giving added support to the concept that the urinary oxalate in this condition as well as in normals is largely derived from endogenous sources. Early reports suggested that glucose (42), uric acid (43), or pyrimidines (44) were sources of urinary oxalate. Although these studies have not been confirmed, glycine, glyoxylic acid, glycolic acid, glycoaldehyde, ascorbic acid and its metabolites, and ethylene glycol may all contribute to urinary oxalate. There is no evidence available in humans or intact animals to confirm the possibility that acetoacetate, Krebs cycle intermediaries, or pentose sugars are a direct source of urinary oxalate. Archer et al. (15) summarized the available knowledge of the precursors of urinary oxalate and theorized that the disorder of oxalate metabolism centered about an abnormal conversion of glycine to oxalate. They were able to show in a patient a partial lessening of urinary oxalate excretion by an attempt to deplete the "pool of available glycine" by administering oral benzoate. Our own studies showed a possible slight lowering of oxalate excretion during three days on high benzoate intake in a normal subject, but there was no depression of oxalate excretion in

the patient with hyperoxaluria. If the hypothesized block between glyoxylic acid and glycine does exist as the basic defect in hyperoxaluria, serine might serve as a major source of urinary oxalate. Such a pathway appears possible in both normal and hyperoxaluric subjects; serine might serve as the link in intermediary metabolism through which carbon atoms derived from glycogen and glucose might eventually be directed toward oxalate.

Relationship of Pyridoxine: The studies of Gershoff, Faragalla, Nelson, and Andrus (25, 26) have demonstrated a consistent but undefined relationship between vitamin B deficiency in cats and rats and the occurrence of oxalate nephrocalcinosis and hyperoxaluria. When pyridoxine supplements were given to humans, a decreased oxalate excretion resulted, even though the diets were thought to be more than adequate in vitamin B₆ content. A combination of vitamin B₆ and folic acid decreased the urinary oxalate by 58%, whereas vitamin B₆ alone decreased urinary oxalate by 25% (16). Although the site of pyridoxine's effect on oxalate metabolism has not been defined, it is known that vitamin B₆ is a necessary cofactor in transamination reactions. It has been shown by Cammarata and Cohen (45) that vitamin B₆ is important in the transamination reaction between glyoxylic acid and glycine. Thus, it appears possible that the addition of excess amounts of vitamin B₆ to the diet of normal patients might speed up this transformation reaction, thereby throwing the equilibrium further in the direction of glycine production. This possibility forms the basis for attempting to use pyridoxine to treat patients with hyperoxaluria.

Relationship of Ascorbic Acid: With both chemical and radioisotopic methods it has been shown that ascorbic acid may be converted to oxalic acid as a metabolic end product. An average of 44% of L-ascorbic acid-1-C¹⁴ administered to humans was excreted as urinary oxalate (21). Lamden

and Chrystowski (20) administered an increasing amount of ascorbic acid to 40 normal humans, who showed a significant increase in urinary oxalate excretion when more than 4 g of ascorbic acid were given orally.

Relationship of Uric Acid Metabolism: Aponte and Fetter (2) noted an elevation of uric acid in each of their three cases of hyperoxaluria, and Edwards (14) recorded a serum uric acid level of 11.8 mg per 100 ml. These increased uric acid levels seemed higher than could be explained by coexisting renal failure; elevation of uric acid was recorded by Shepard et al. (7) in a patient free of uremia, and Case 3 of our series had symptoms compatible with acute gout. The patient with hyperoxaluria reported by Burke, Baggenstoss, Oweil, Power, and Lohr (28) initially passed a uric acid stone, and Hodgkinson (46) reported that a high purine diet caused a rapid rise in the level of oxalate excretion in a patient with hyperoxaluria. While the significance of these observations remains uncertain, gout and hyperoxaluria have a common bond, in that these are the only known inborn errors in which the end product of an intermediary metabolic pathway is excreted in excess and precipitates within the body. Generally, the lack of a necessary enzyme induces a metabolic block which causes precursor metabolites to accumulate. Despite considerable speculation, the unusual accumulation of end-product metabolites in gout and hyperoxaluria have not been related to any specific enzyme block by direct means; perhaps, instead, a failure exists of some feed-back control mechanism to shut off production of these end metabolites.

SUMMARY

Elevated urinary oxalate excretion led to the diagnosis of primary hyperoxaluria in four patients. The milder form of the disease in these patients is characterized by

the formation and passage of repeated kidney stones and urinary tract infection. An elevation of urinary oxalate is the only laboratory abnormality of note. Progressive renal failure, hypertension, and uremia with its disturbances in growth and nutrition have not occurred as in more severe cases.

Interrelationships between various pathways of intermediary metabolism leading to oxalate formation are discussed in detail. It is suggested that oxalate emerges as a side product from a cycle including glyoxylic acid, glycine, serine, and glycolic acid.

Therapy should be directed toward the control and elimination, if possible, of urinary tract infection. Long-term pyridoxine therapy has failed to achieve a significant lowering of oxalate excretion, but trials with this therapy should be continued.

SUMMARY IN INTERLINGUA

Le constatación de elevate excretion urinari de oxalato esseva responsabile in quatro patientes pro le establimento de un diagnose de hyperoxaluria primari. Le forma plus tosto leve del morbo in iste patientes es characterisate per le formation e vacuation repetite de calculos renal e per le occurrentia de infection del vias urinari. Le elevation del oxalato urinari es le sol anomalitate laboratorial de nota. Per contrasto con lo que occorre in casos grave, nulle progressive disfallimento renal, nulle hypertension, e nulle uremia (con le normalmente associate disturbationes de crescentia e de nutrition) esseva constatate in le presente casos. Es discutate in detalio le relationes inter le varie circuitos de metabolismo intermediari que resulta in le formation de oxalato. Es presentate le conception que oxalato resulta como producto lateral in un cyclo que include acido glyoxylic, glycina, serina, e acido glycolic. Le therapia debe esser orientate verso le compensation e elimination (in tanto que possibile) del infection del vias urinari. Therapia a longe vista con pyridoxina non ha resultate in un significative reduction del excretion de oxalato, sed essayos con iste forma de therapia deberea esser continuare.

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A Genetic Study of Two Families Having the Acute Intermittent Type of Porphyrria

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THE PREVALENCE OF ACUTE INTERMITTENT PORPHYRIA is greater than has been supposed, as a number of recent authors have emphasized (1-4), because so many cases with clinical expression of this disease are misdiagnosed, while almost all of the latent cases remain undetected. Recognition of the latent carriers of this genetic disease is of the utmost importance, since undiagnosed cases are in constant danger of taking, or of being given, barbiturates or other drugs that may precipitate or aggravate acute attacks and may result in permanent neurologic damage or even in death. Furthermore, when an acute attack develops, whether spontaneously or due to drug induction, the unrecognized porphyric patient is frequently subjected to needless surgical operations, which are usually preceded or accompanied by barbiturates for sedation or anesthesia.

This report concerns a genetic study of two porphyric families. The urine of each member studied was tested for porphobilinogen (PBG) by the qualitative Watson-Schwartz test (5). In addition, quantitative measurements were made of the daily urinary excretion of the two porphyrin precursors, delta-aminolevulinic acid

(δ ALA) and porphobilinogen, as well as the two urinary porphyrins, uroporphyrin and coproporphyrin.

The first family, Family Zu., consisting of 15 persons embracing four different generations, is of special interest for the following reasons:

1. A greater percentage of persons shows the genetic metabolic defect than in any family previously reported.

2. The male members of the family display greater expressivity, that is, they appear to be more severely affected by the metabolic defect as judged by the quantitative excretion of porphyrins and porphyrin precursors than do the female members, in contrast to most series of cases of manifest or latent acute intermittent porphyria.

3. Consistently negative colorimetric qualitative tests for porphobilinogen (Watson-Schwartz tests) were obtained on one 24-hour urine specimen collected from an apparently healthy brother of the proband, despite the presence of large amounts of porphobilinogen in that urine when it was measured quantitatively following column chromatography. Positive Watson-Schwartz tests were found in all other 24-hour urine samples obtained from him.

4. Increased urinary excretion of various indolic compounds, especially 5-hydroxy-indoleacetic acid, was found in six of 15 members of the family.

The second family, Family St., is noteworthy because the discovery of the disease in the family was made by one of its own members, a laboratory technician. Having detected the metabolic defect in herself, she was able to make a correct diagnosis of

Received for publication January 12, 1961.

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This work was supported in part by U. S. Public Health Service Grant A-2872 for Studies of Porphyrin Metabolism.

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porphyria in her sister, who had been diagnosed as having schizophrenia and had spent three years in a psychiatric hospital.

MATERIALS AND METHODS

Urine for a full 24-hour period from each person in the family available for study was collected in brown bottles containing 25 ml of petroleum ether and 5 g of sodium carbonate. The samples were refrigerated until all assays were completed. A Watson-Schwartz test was performed according to the original method of Watson and Schwartz (5) upon receipt of the urine in the laboratory; the quantitative assays of the porphyrin precursors and the porphyrins were made within 24 to 48 hours of excretion. When a positive Watson-Schwartz test was obtained, the sample was then tested for butanol extractable chromogen, since we have confirmed the observation of Schwartz and Watson (6) that most substances yielding false-positive reactions are extractable by butanol, whereas

porphobilinogen is not. Porphobilinogen and delta-aminolevulinic acid were measured spectrophotometrically, according to the method of Mauzerall and Granick (7), following adsorption on and elution from Dowex-2 and Dowex-50 resin columns, respectively. Uroporphyrin was extracted and measured spectrophotometrically, according to the method of Rimington and Sveinsson (8), with the corrections for extinction given by With (9). Coproporphyrin was measured fluorimetrically according to the method of Schwartz, Zieve, and Watson (10). Each quantitative measurement was made in duplicate. When an equivocal result was obtained, or when there was an increased excretion of one precursor or porphyrin without accompanying increase in the others, a second 24-hour urine specimen was collected and the measurements were repeated.

Urinary indoles were measured by the two-dimensional paper chromatographic method of Jepson (11). The method of Udenfriend, Titus, and Weissbach (12) was used for the quanti-

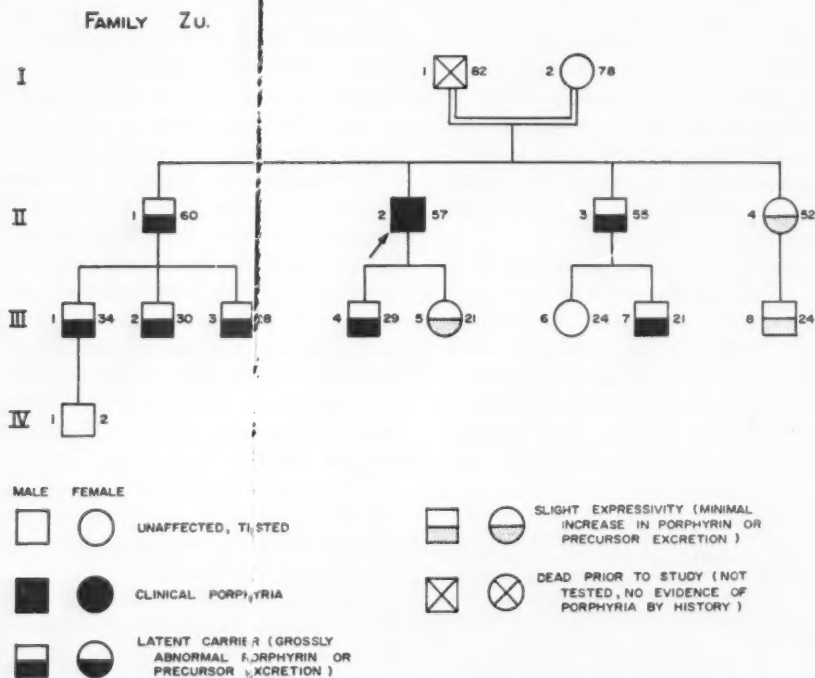


FIGURE 1. The number to the left of each symbol indicates position in the sibship; the number to the right of each symbol indicates the age of the individual at the time the study was made. The arrow indicates the proband.

TABLE 1. Urinary Excretion of Porphyrins and Precursors by Members of Family Zu

Subject	Age (yr)	Date	Volume (ml)	Watson-Schwartz (0 to +4)	PBG mg/day	δ ALA mg/day	URO mg/day	COPRO μ g/day	5-HIAA mg/day
Normal values				0	0.5-1.5	1-3	.05	150-300	2-10
I-2 (R. Z.)	78	11/8/57	1,190	0	—	—	.07	204	—
		11/9/57	1,000	0	—	—	.04	140	—
II-1 (H. Z.)	60	5/1/57	—	+4	—	—	.32	—	—
		3/26/59	850	0	16.10	4.45	.60	1,010	14.5
		10/23/59	740	+4	11.70	7.36	.37	—	—
II-2 (C. Z.)	57	4/1/57	—	+4	—	—	1.80	—	—
		3/12/59	2,060	+4	64.90	31.29	1.63	1,975	11.0
		5/27/60	825	+4	51.90	16.50	1.14	712	14.0
		5/28/60	1,100	+4	42.60	30.20	3.80	1,963	—
		5/29/60	1,570	+4	48.10	25.90	2.65	1,588	—
		5/30/60	1,600	+4	40.90	21.20	1.36	1,218	—
		5/31/60	1,500	+4	52.00	25.80	1.92	1,642	—
		6/1/60	1,380	+4	44.00	11.80	1.76	1,477	—
		6/2/60	1,270	+4	42.30	23.20	2.36	1,466	—
II-3 (Sa. Z.)	55	4/26/59	1,200	+4	18.12	12.57	.67	1,310	13.3
II-4 (B. F.)	52	4/20/59	820	+3	.37	2.14	.05	280	12.5
		6/10/59	600	+1	1.62	1.57	.07	—	—
		12/10/59	1,220	+1	0.54	2.23	.02	—	—
III-1 (St. Z.)	34	5/5/59	860	+2	1.54	3.82	.05	376	—
		7/6/59	1,000	+2	2.70	4.97	.06	—	—
III-2 (Mv. Z.)	30	5/5/59	1,280	+3	.57	3.35	.13	617	—
III-3 (Ro. Z.)	28	4/26/59	1,680	+1	3.39	4.40	.11	374	12.4
		7/6/59	1,630	+2	1.46	4.27	.05	417	—
III-4 (Si. Z.)	29	3/29/59	1,660	+3	5.10	4.34	.19	560	10.6
III-5 (Ri. Z.)	21	4/12/59	850	+1	2.29	2.22	.04	310	4.3
III-6 (E. Z.)	24	3/26/59	980	0	0.44	1.28	.05	397	5.6
		10/23/59	540	0	1.09	2.40	.05	—	—
III-7 (J. Z.)	21	4/21/59	1,240	+2	4.17	5.41	.23	520	13.8
III-8 (M. F.)	24	5/25/59	1,260	+3	6.22	3.30	.12	300	—
		2/7/60	1,000	+2	2.25	1.96	.07	—	—
IV-1 (Ha. Z.)	2	5/5/59	200	0	0	.26	.01	50	—

Legends:

PBG: porphobilinogen.
 δ ALA: delta-aminolevulinic acid.
 URO: uroporphyrin.
 COPRO: coproporphyrin.
 5-HIAA: 5-hydroxyindoleacetic acid.

tative measurement of 5-hydroxyindoleacetic acid.

STUDIES IN FAMILY ZU.

This pedigree (Figure 1) comprises 14 members of three generations and a child of the fourth generation. Only one mem-

ber, the proband, has had a manifest acute attack of porphyria, despite the apparently constant excretion of large quantities of porphyrin precursors and porphyrins by many other members of the family. A brief clinical description of Case 1, the proband (II-2, Figure 1), follows.

CASE 1 (C.Z.)

In March, 1957, this 57-year-old white man complained of pain in the scrotum. This was attributed to an inguinal hernia, and a herniorrhaphy was performed at a community hospital. The pain persisted, however, and one week later he developed severe lower abdominal pain. He was again admitted to the hospital, and an exploratory operation was performed. It was reported that some adhesions were lysed and a normal appendix was removed. Pain persisted and the patient became psychotic. He was admitted to a psychiatric hospital and was given three electroshock treatments. In addition to the mental changes, the patient now showed neurologic signs consisting of loss of deep tendon reflexes in all four extremities, weakness of the abdominal muscles and the extensor muscles of both forearms, and ataxia that was attributed to weakness rather than to a specific neurologic lesion. It was discovered that his urine contained large amounts of porphobilinogen, as shown by a strongly positive Watson-Schwartz test. The excretion of uroporphyrin was 1.8 mg per 24 hours, greatly exceeding maximum normal values (0.05 mg per 24 hours). It was ascertained that the patient had been given barbiturates at the time of each operation.

He recovered from the psychotic episode, and since that time has had no recurrence of mental aberration, neurologic symptoms or signs, or abdominal pain, despite the constant excretion of large amounts of δ ALA, PBG, uroporphyrin, and coproporphyrin (Table 1). There has been no increase in the concentration of protoporphyrin or coproporphyrin in the feces.

EXCRETION OF PORPHYRINS AND PRECURSORS
BY OTHER MEMBERS OF THE FAMILY

The parents of the proband were first cousins, but neither had ever manifested symptoms or signs of acute intermittent porphyria; nor was there a history of the

disease in any of their ancestors or collateral relatives. On three separate occasions, the urine from the mother of the proband (I-2 Figure 1 and Table 1) showed no abnormal amounts of porphyrins or precursors. She died at the age of 78 of a cerebral hemorrhage. There was no opportunity to study the father of the proband (I-1), since he was killed in an automobile accident shortly before the studies described here were made. He was 82 years old at the time of his death.

In Table 1 it is shown that both brothers of the proband excreted greatly increased quantities of delta-aminolevulinic acid and porphobilinogen, uroporphyrin, and coproporphyrin. Neither has manifested any signs or symptoms of porphyria. In contrast to the male members of this generation, a sister of the proband (II-4) displayed little evidence of increase in urinary porphyrins or precursors, and no symptoms of the disease. However, a 3+ (moderately positive) Watson-Schwartz test was obtained on one occasion, despite a quantitative measurement of porphobilinogen showing no increase. Two subsequent 24-hour urine specimens from this woman confirmed the earlier results showing no quantitative increase in porphyrins or precursors despite slight, but definitely positive, Watson-Schwartz tests. The chromogen was not completely extractable by butanol. Two-dimensional paper chromatography and colorimetric procedures showed an increased amount of certain indoles in this woman's urine (see below). These indoles may have contributed to the positive Watson-Schwartz tests. However, it is believed that she must have possessed the defective gene for porphyria because she apparently transmitted it to her son, whose urine showed not only positive Watson-Schwartz tests but slightly increased excretion of porphobilinogen, delta-aminolevulinic acid, and uroporphyrin.

The spouses of each of the siblings of generation II are not shown in Figure 1

because there was nothing to indicate that any of them possessed a defect in porphyrin metabolism. The wife of the proband had died before this study was made. The cause of death was rheumatic heart disease, and there was no history suggesting porphyria. The spouses of II-1, II-3, and II-4 showed no clinical evidence of porphyria, and urine samples from each of them showed no abnormal excretion of porphyrins or precursors.

In the third generation each of the six male members is obviously affected, showing consistently positive Watson-Schwartz tests, as well as increases in the quantitative excretion of δ ALA, PBG (with but one exception), and in most cases slight increases in both uroporphyrin and coproporphyrin. On the other hand, only one (III-5) of the two female members of this generation, both in their early twenties, displayed a positive Watson-Schwartz test and slight increases in δ ALA and PBG.

URINARY EXCRETION OF INDOLES IN FAMILY ZU.

A more intensely positive Watson-Schwartz test than was indicated by the quantitative amount of porphobilinogen excreted by II-4 prompted us to measure urinary indoles, since it had been shown previously by one of us that indoles may cause false-positive Watson-Schwartz tests (13). A two-dimensional paper chromatogram of the first 24-hour urine specimen collected from II-4 showed spots indicating the presence of the following indolic compounds: indican, 6-hydroxyskatole (6-HS), indoleacetic acid (IAA), tryptophan, and 5-hydroxyindoleacetic acid (5-HIAA). Only the indican, 5-HIAA, and tryptophan spots were quantitatively increased; the others fell within the usual range found in urine from normal subjects. Measurement of another 24-hour urine specimen from II-4 again showed increased 5-hydroxyindoleacetic acid. Consequently, urinary indoles were measured in other members of the

family. An increased amount of indolic compounds was found in chromatograms of urine from five of the 16 members (II-1, II-2, II-4, III-1, and III-2, Table 1).

While some showed increased indican, 6-hydroxyskatole, and tryptophan, the most noticeable increase was in 5-hydroxyindoleacetic acid. Quantitative measurement of 5-HIAA gave higher than normal excretion, varying between 11 and 17 mg per liter or 11 and 14.5 mg per day, in six of the nine members of the family upon whom quantitative assays were made (II-1, II-2, II-3, II-4, III-3 and III-7, Table 1).

STUDIES IN FAMILY ST.

CASE 1

The proband (II-4, Figure 2) in Family St. is a 27-year-old white female laboratory technician. In 1957, while demonstrating to student laboratory technicians the performance of a Watson-Schwartz test, she discovered that her own urine contained large amounts of porphobilinogen.

She had never experienced an attack of acute abdominal pain or any of the neurologic symptoms or signs characteristic of acute porphyria, although subsequent studies have shown that she consistently excretes increased quantities of porphyrins and precursors, and the Watson-Schwartz test has repeatedly been found to be strongly positive.

The following history was obtained from II-4 and the physicians that she had consulted prior to 1957: In 1954 she developed pitting edema of both ankles. She was examined and found to have an enlarged liver that was palpable 2 cm below the right costal margin. Hepatic function tests were within normal limits. There was 9% retention of bromsulfalein in the serum 45 minutes after injection of the dye. Between November 1954 and June 1955 she consulted a psychiatrist, who made a diagnosis of anxiety neurosis. In March and May 1957 she was again examined and the liver was palpated 3 to 4 cm below the

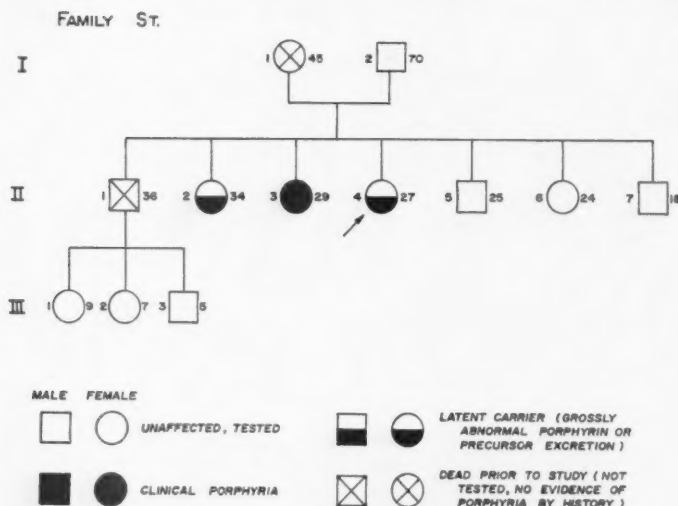


FIGURE 2. The number to the left of each symbol indicates position in the sibship; the number to the right of each symbol indicates the age of the individual at the time the study was made. The arrow indicates the proband.

right costal margin. She was asymptomatic and had no other abnormal physical signs. Hepatic function tests were normal except for 18% and 14% bromsulfalein retention 45 minutes after injection of the dye. The serum cholesterol concentration was also increased to 400 mg per 100 ml.

When examined by one of us (GDL) in December 1957 there were no abnormal symptoms or signs except that the liver was felt 3 cm below the right costal margin. Hepatic function tests showed some abnormalities, consisting of 11% retention of bromsulfalein in 45 minutes, thymol flocculation 3, and thymol turbidity, 3+. Cephalin-cholesterol flocculation was negative, and zinc turbidity was 4.3. Serum bilirubin was 0.59 mg per 100 ml, with 0.16 mg per 100 ml of the direct reacting variety. Serum cholesterol was 355 mg per 100 ml; cholesterol esters were 279 mg per 100 ml. The concentrations of serum phospholipids, fatty acids, fasting glucose, total protein, albumin, and globulin were all within normal limits, and the electropho-

retic pattern of serum proteins was normal. The blood urea nitrogen was 16 mg per 100 ml.

She has remained well and has been able to work daily since that time. Measurements of urinary porphyrins and precursors have been made at intervals (Table 2).

CASE 2

A sister of the proband, II-3, age 29, is the only member of this family known to have manifested the acute abdominal pain and psychiatric symptoms characteristic of acute intermittent porphyria. While serving in one of the armed services in 1953, she developed frequent headaches that were centered in the temporal or frontal regions. Following attempted suicide, a diagnosis of undifferentiated schizophrenia was made. She was placed in a military hospital for four months, then discharged from the armed services and sent to a veterans administration hospital, where a diagnosis of schizophrenia was said to have been confirmed.

During the succeeding three years she was treated with electroshock, insulin shock, and tranquilizing drugs. In retrospect, during this period she had one episode of paralysis of bowel and bladder function during which she noted that her urine turned a dark mahogany color upon standing. However, porphyria was not suspected. She was discharged from the psychiatric service of the veterans hospital in 1956. She consulted a psychiatrist during the ensuing year, but received no treatment other than psychotherapy. In 1957 she entered the school of nursing of a large eastern university medical center, and in 1960 successfully completed her training as a nurse. During this period, she was admitted to the hospital on two separate occasions for colicky pain in the lower abdomen, accompanied by headache, constipation, and tachycardia. These attacks occurred at the mid-point of her menstrual cycle. No other factors that might have precipitated the acute attacks were identified.

Excretion of porphobilinogen and porphyrins was greatly increased at these times (Table 2), although excretion of both precursors and porphyrins was abnormally high each time it was measured, even when she was free of symptoms. Her liver has never been palpable, and there have been no other abnormal physical signs. During the acute attacks of porphyria, the cephalin-cholesterol flocculation was 2+, and the retention of bromsulfalein was 13% in 45 minutes. Serum cholesterol was 392 mg per 100 ml; cholesterol esters were 300 mg per 100 ml. When she had recovered from an acute attack and was free of symptoms, the cephalin-cholesterol flocculation was reduced to 1+, bromsulfalein retention was reduced to 6%, and total serum bilirubin concentration was 0.37 mg per 100 ml.

OTHER MEMBERS OF FAMILY ST.

The oldest female among the siblings, II-2, age 34, has shown positive qualitative Watson-Schwartz tests for porphobilinogen

TABLE 2. Urinary Excretion of Porphyrins and Precursors by Members of Family St

Subject	Age (yr)	Date	Volume (ml)	Watson-Schwartz (0 to +4)	PBG mg/day	δ ALA mg/day	URO mg/day	COPRO μ g/day
Normal values				0	0.5-1.5	1-3	.05	150-300
I-2 (S. S.)	70	2/19/58	1,040	0	—	—	.041	—
II-2 (R. S.)	34	1/17/58	1,000	+3	9.1	—	.152	290
II-3 (Mi. S.)	29	11/15/57	2,000	+4	37.8	—	1.160	710
		11/20/57	1,950	+4	26.3	—	.650	—
		2/10/58	1,800	+4	50.0	—	.830	—
II-4 (K. S.)	27	12/14/57	1,280	+4	37.3	3.90	.790	400
		7/16/58	2,125	+4	23.0	—	.380	520
II-5 (W. S.)	25	2/18/58	Random sample	0	—	—	—	—
II-6 (Ma. S.)	24	2/18/58	Random sample	0	—	—	—	—
II-7 (R. S.)	18	2/18/58	Random sample	0	—	—	—	—
III-1 (V. S.)	9	1/17/58	290	0	—	—	.010	—
III-2 (D. S.)	7	2/24/58	280	0	—	—	.011	—
III-3 (T. S.)	5	2/18/58	310	0	—	—	.012	—

Legend: See Table 1.

on repeated occasions, but has never had symptoms or signs of acute porphyria. One brother (II-5), age 25, gives a history of attacks of abdominal pain, but repeated qualitative examinations of his urine for porphobilinogen during intervals without symptoms have been reported to be negative. The other siblings tested have shown negative Watson-Schwartz tests and have had no attacks suggestive of acute porphyria. One brother, (II-1) age 36, was considered to be alcoholic and was reported to have had cirrhosis of the liver. He was killed in an automobile accident before porphyria was discovered in the family. Urine specimens from his three children, who are all under ten years of age, have been examined. They have been found to be negative in the qualitative screening test for porphobilinogen and have been shown to have normal quantitative excretion of uroporphyrin (III-1, III-2, and III-3, Table 2).

There was no blood relationship between the parents of the proband. The father of the proband is living at the age of 70. His urine gives a negative Watson-Schwartz test, and quantitative uroporphyrin excretion is within normal limits. The mother of the proband had asthma for years but no symptoms or signs to suggest porphyria. She had died at the age of 45 from pneumonia. It is presumed that she was the carrier.

Paper chromatograms for indolic compounds showed that there was no abnormal urinary excretion of indoles by any of the six members of Family St. who were tested.

DISCUSSION

MODE OF GENETIC TRANSMISSION

The acute intermittent type of porphyria has been shown to be inherited as an autosomal mendelian dominant trait (1, 14). Both families presented here appear to follow this pattern. Family Zu. is unique among reported pedigrees because of the

high proportion of the members of the family showing the metabolic defect when biochemical criteria are used for detection, and because of the apparent preponderance of affected males. However, a sex-linked dominant or recessive defect can be excluded by a study of the pedigree. An ideogram of leukocytes obtained from the proband and grown in tissue culture showed no gross chromosomal aberration.* The fact that there is a preponderance of males in the pedigree may help to explain the greater number of males being affected. But there may also be variable expressivity; the biochemical defect may become more severe and manifest in the females later, especially in view of the apparent deleterious effect of the menstrual cycle or of pregnancy in some cases of acute intermittent porphyria.

On the other hand, there may be some factor leading to greater expression of the metabolic abnormality in the male members of this family. It is noteworthy that the father and mother of the proband (first generation in Figure 1) were first cousins. However, no definite evidence was obtained that this relationship contributed to a greater number of persons in the pedigree being affected than is usually found, since the mother (I-2) showed no abnormality of porphyrin excretion and no clinical evidence of the disease. That she might have carried the abnormal gene without its being penetrant is a remote possibility that cannot be excluded. However, the results of Haeger's study (15) of many Swedish porphyric families suggest that only those who display increased excretion of porphyrins or precursors transmit the disease. Although there was no clinical expression of the disease in the father, biochemical expression cannot be excluded, since he could not be studied. The probability is greater that he was the carrier. A

* These studies were made by Dr. Paul Morehead of the Wistar Institute.

possible explanation for a greater proportion of persons being affected in this pedigree than in any previously reported is that the parents both came from a geographic isolate in Russia. A common genetic substrate may have contributed toward greater penetrance and expression of the abnormal gene. There exists the further possibility that consanguinity may have contributed modifying genes, leading to a greater expressivity.

FALSE-NEGATIVE AND FALSE-POSITIVE WATSON-SCHWARTZ TESTS

The finding of a consistently negative Watson-Schwartz test in one 24-hour urine specimen collected from II-1 (Family Zu.), despite the presence of greatly increased quantities of porphobilinogen (18 mg per day), deserves comment. It is presumed that some inhibitor to the reaction between porphobilinogen and Ehrlich's reagent (paradimethylaminobenzaldehyde) was present in the urine, and that it was removed by chromatography of the urine on a Dowex-2 resin column. It has been reported that urea may interfere with this reaction (7, 16). However, by paper chromatography, there appeared to be no great excess of urea in this urine sample. We were unsuccessful in identifying the cause of the negative reaction. Serial dilution of the urine failed to yield a positive reaction. Yet previous and subsequent 24-hour urine specimens from this man always yielded intensely positive (4+) Watson-Schwartz tests, in good agreement with the quantitative amount of porphobilinogen present, as determined spectrophotometrically following column chromatography. On two other occasions we have obtained negative Watson-Schwartz tests on urine from latent porphyrics (not reported here) despite excretion of grossly abnormal quantities of PBG (to 10 mg per day). Nevertheless this finding has been rare in our experience. Its only significance is to suggest that the simple qualitative Watson-Schwartz test is not

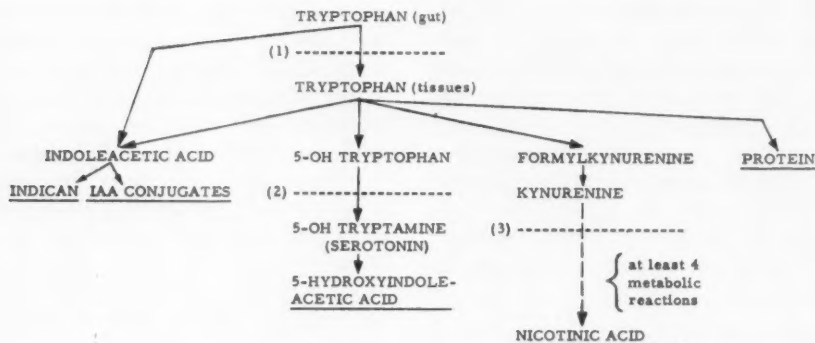
always sufficient in genetic studies to determine whether an asymptomatic carrier has the biochemical defect. Moreover, we have occasionally found definitely false-positive Watson-Schwartz tests not due to PBG in studies of relatives of other patients who have porphyria. This shows the need for more detailed biochemical studies, such as those presented here and those reported from Waldenstrom's Clinic (14) to determine patterns of genetic transmission of the metabolic defect and the degree of penetrance of the abnormal gene.

SIGNIFICANCE OF INDOLURIA

The significance of the slight but definite increase in urinary excretion of 5-hydroxy-indoleacetic acid and other indoles in some members of Family Zu. is not known. There was no history of ingestion of bananas or other fruits containing serotonin that might have accounted for the increased 5-HIAA excretion. It is quite possible that the indoluria is related to constipation, which is so common in acute intermittent porphyria and which may be present in latent carriers. On the other hand, there is other evidence to suggest that indoluria might be related to an interference with tryptophan metabolism. In general, indole excretion was highest in those who showed the greatest increase in excretion of porphyrins and precursors (Table 1).

Abnormal urinary excretion of indolic compounds has been found to accompany three other inborn errors of metabolism, namely phenylketonuria (17), Hartnup disease (18), and "maple syrup urine" disease (19). In all of these diseases, indoluria is considered to be secondary to other metabolic faults (20), and it would seem to be certain that this is true in the family having porphyria described in this report.

We first considered the possibility that indoluria might be produced by a mechanism similar to that which results in indoluria in phenylketonuria, especially in view of the finding reported by Mellincoff, Hal-



SCHEMATIC SUMMARY OF THE MAIN METABOLIC PATHWAYS OF TRYPTOPHAN

FIGURE 3. (1) Postulated defect in absorption or transport of tryptophan by intestinal mucosal cells, and perhaps by hepatic and renal tubular cells in Hartnup disease (28); (2) Postulated inhibition of tryptophan-serotonin pathway by phenylalanine metabolites in phenylketonuria (23-25); (3) Postulated block of tryptophan-nicotinic acid pathway shown by Price et al. (27) in porphyria. Blocks in the sites indicated could explain increased production and excretion of indoles that have been described in Hartnup disease and in phenylketonuria, and those occurring in the porphyric family reported here.

pern, Frankland, and Greipel (21) that aminoaciduria frequently accompanies acute intermittent porphyria, with phenylalanine being one of the amino acids most consistently increased in the urinary chromatograms. In phenylketonuria, there is increased excretion of indoleacetic and indoleacetic acids (17) and indican (22). However, 5-hydroxyindoleacetic acid excretion is decreased in conformity with a decreased circulating 5-hydroxytryptamine (serotonin) concentration and a decreased conversion of exogenous 5-hydroxytryptophan (5-HT) to serotonin (23, 24). The latter findings led to the suggestion that phenylalanine or one of its metabolites that accumulate in phenylketonuria might inhibit serotonin formation and thus divert tryptophan to the formation of other indolic compounds that are excreted in excess. Davison and Sandler (25) then demonstrated, *in vitro*, that 5-HT decarboxylase, the enzyme that catalyzes the conversion of 5-HT to serotonin, is inhibited by phenylacetic, phenylpyruvic, and phenyllactic acids, all of which could accumulate in phenylketonuria

(note metabolic block at (2) in Figure 3). On the other hand, Tashian (26) has shown that phenylacetic, *o*-hydroxyphenylacetic, and phenylpyruvic acids, when administered orally to healthy control subjects, produced consistent increases in urinary indoleacetic acid excretion, but little change or a slight increase in 5-HIAA excretion. Therefore, the precise mechanism of increased production and excretion of indoles in phenylketonuria remains unexplained.

The fact that 5-hydroxyindoleacetic acid excretion was increased in many members of the family having porphyria reported here whereas it is decreased in phenylketonuria (23, 24) suggests that the mechanism of increased production and excretion of indoles must be different from that which obtains in phenylketonuria. Furthermore, the proband in Family Zu. did not show aminoaciduria during a period of remission, even when 5-HIAA excretion was increased, and aminoaciduria was not present in other members of the family who were tested.

Another possibility that might better explain indoluria in some porphyric patients is the observation of Price, Brown, and Peters (27) that there is an abnormality of tryptophan metabolism in porphyria. They showed increased excretion of kynurenine and other metabolites between tryptophan and nicotinic acid in 13 of 18 porphyric subjects. Although this excretion pattern resembles that which accompanies pyridoxine deficiency, administration of this vitamin did not alter the defect. Therefore, the authors postulated that there is a functional or apparent pyridoxine deficiency resulting from imbalance in the polyvalent cations required for pyridoxal phosphate to function as a coenzyme. Whether or not this is the correct explanation of the mechanism, one might speculate that the presence of such a block could lead to diversion of tryptophan from this pathway to the formation of indole compounds (note metabolic block at (3) in Figure 3). Thus there may well be a link between the abnormality of tryptophan metabolism found in porphyria by Price et al. (27) and our finding of increased urinary excretion of indolic compounds in some porphyrics. A relative block in the tryptophan-nicotinic acid pathway might divert tryptophan to the pathways by which other indolic compounds are formed. An increased excretion of 5-HIAA along with indoleacetic acid and indican could thus be explained.

Studies in Hartnup disease may be relevant to this discussion. In this inborn error of metabolism there is concomitant aminoaciduria and indoluria (18). The indoluria is qualitatively similar to that which occurs in phenylketonuria, except that in Hartnup disease indoleacetylglutamine has been reported to occur along with increased IAA and greatly increased indican. More recently, Milne, Crawford, Girao, and Loughridge (28) showed that there was less conversion of ingested tryptophan to kynurenine in patients who have Hartnup disease than in normal control subjects, and

a much greater increase in excretion of indoleacetic acid and indican. However, the block in tryptophan metabolism was different from that which Price et al. had observed in porphyria. Milne et al. (28) postulate that in Hartnup disease there may be a defect in tryptophan transport in the intestine, kidney, and possibly in the liver (note metabolic block at (1) in Figure 3). This defect would result in conversion by the intestinal bacteria of the unabsorbed tryptophan to indolic compounds, which could be absorbed and subsequently excreted in the urine. Thus the precise mechanism by which tryptophan metabolism is deranged may be different in phenylketonuria, Hartnup disease, and in acute intermittent porphyria; yet each could lead to increased indole excretion.

Some cases of acute intermittent porphyria exhibit hyponatremia and hypochloremia, which has been attributed to a renal tubular defect (29-31). It is tempting to relate all three defects, namely aminoaciduria, indoluria, and the electrolyte abnormalities, to a common renal origin. However, a recent study of three cases of acute porphyria accompanied by hyponatremia and hypochloremia (32) suggests that the electrolyte abnormalities occur only when there is concomitant central nervous system involvement and that they resemble those present in syndromes in which there is thought to be an inappropriate secretion of antidiuretic hormone (33, 34) rather than a primary renal defect.

It is doubtful that either aminoaciduria or indoluria is a primary or a very important defect in porphyria. However, the findings of Mellincoff et al. (21) and those reported here suggest that further study of the excretion of these substances in acute intermittent porphyria is warranted.

SUMMARY

1. Quantitative studies of the urinary excretion of uroporphyrin, coproporphyrin, and the porphyrin precursors, delta-

aminolevulinic acid and porphobilinogen, are reported in two families having acute intermittent porphyria.

2. In the first family, ten of the 13 relatives of the proband were found to be latent carriers of the metabolic defect. In the second family, two siblings of the proband, out of ten persons examined, were found to possess the defect.

3. In both pedigrees, the metabolic defect appeared to be transmitted as a mendelian dominant autosomal trait.

4. In some instances, gross discrepancies were found between the Watson-Schwartz test and the quantitative assay of porphobilinogen present in the urine.

5. Increased excretion of indolic compounds was found in six of 15 members of one family. Possible reasons for indoluria are discussed.

6. The need for quantitative measurements of porphyrins and precursors in genetic studies of porphyria is emphasized.

ACKNOWLEDGMENT

The authors are indebted to Dana Wontorsky for her invaluable technical assistance.

SUMMARIO IN INTERLINGUA

Esseva effectuate studios genetic de duo familias con porphyria del acute typo intermittente. Mesurationes quantitative del excretion urinari de uroporphyrina e coproporphyrina e del duo precusores de porphyrina, acido delta-amino-levulinic e porphobilinogeno, esseva executate a parte le tests qualitative de Watson-Schwartz pro porphobilinogeno. In un del duo familias, dece de 13 consanguineos del probando esseva recognoscite como portatores latente del defecto metabolic. In le altere familia, duo frateros del probando esseva afficite ex un total de dece personas examine. Il pareva que le defecto esseva transmittite como un dominante character autosomal mendelian. Augmentos del excretion urinari de compositos indolic, specialmente de acido 5-hydroxyindolacetic, esseva constatate in multe membros de un del duo familias. Indoluria pote esser explicate per un bloco in le via ab tryptophano ad acido nicotinic, con le shuntage de tryptophano a vias alternative que resulta in le production de indoles. Un bloco in le via ab tryptophano ad

acido nicotinic in casos de porphyria ha previeamente essite describe per altere autores. Discrepantias inter le tests de Watson-Schwartz e le valores quantitative esseva trogate in certe casos. Es sublineate le desiderato, in studios genetic, de effectuar studios quantitative de porphyrina pro deteger latente portatores de porphyria.

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Physiologic Evaluation and Treatment of Kyphoscoliotic Patients

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NEW TECHNIQUES OF INVESTIGATION have clarified the nature of the abnormalities of pulmonary function in patients with severe kyphoscoliosis. Restricted lung volumes, alveolar hypoventilation, hypercapnia, arterial oxygen unsaturation, and normal distribution of inspired air have been observed in these patients. However, arterial oxygen unsaturation when it occurs is unusually large for the degree of alveolar hypoventilation. Previous investigations have eliminated a diffusion abnormality (1) or atelectasis as a basis for this defect. The present study is concerned with the problem of arterial oxygen unsaturation and with the therapy of the acutely ill kyphoscoliotic patient.

PATIENTS AND METHODS

PATIENTS

Three male and four female patients with severe chest deformities were studied. Their clinical status is described in Table 1. All of them except J. R. were over 50 years of age. Two patients had congenital kyphoscoliosis. Two had acquired the disease after poliomyelitis and two after fracture dislocations. One patient had senile kyphosis. The angles of kyphosis ranged from 45° to 59°, and those of scoliosis from

0° to 115° (1). Onset of the deformity varied from birth to 65 years. Six patients described dyspnea on mild exertion, and two of these observed dyspnea at rest. J. R. and H. M. had chronic respiratory complaints described as being asthmatic attacks. Clinical signs of chronic cor pulmonale with congestive heart failure were observed in five patients.

METHODS

The vital capacity, its subdivisions, and the maximal inspiratory and expiratory flow rates were measured with a 13 liter spirometer and were recorded on a kymograph with slow and rapid speeds. Maximal breathing capacity was performed by inspiring from a 120 liter spirometer through a low resistance valve. Distribution of inspired air was measured with a nitrogen meter* using the single breath test of Comroe and Fowler (2) or the concentration of nitrogen in alveolar gas after seven minutes of oxygen breathing (3, 4). Expired gas for measurement of respiratory rate, tidal volume, and minute volume of ventilation was collected in a Douglas bag. During the collection of expired gas, arterial blood samples (brachial artery) were obtained during ventilation with room air at rest. In four patients arterial blood samples were also collected after ventilation with 99.6% oxygen at rest. Arterial blood oxygen content and capacity, and carbon dioxide content were measured by the method of Van Slyke and Neill (5). Correction was made for drainage and hemoconcentration during tonometer equilibration of the samples (6) by spectrophotometric determination of cyanmethemoglobin of both content and capacity samples. The arterial blood carbon dioxide tension was derived by applying the line charts of Van Slyke and Sendroy (7) to the blood pH and plasma carbon dioxide content. Oxygen and

Received for publication March 4, 1961.

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Supported in part by U. S. Public Health Service Grant No. H-3795 (C2).

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* Nitralyzer Model 300AR: Custom Engineering and Development Co., St. Louis, Missouri.

TABLE 1. Physical Characteristics and Clinical Data

Patient	Age (yr)	Sex	Height (cm)	Body Surface Area (m ²)	Etiology	Age at Onset	Degree of Scoliosis*	Degree of Kyphosis*	Dyspnea	Cor Pulmonale and Heart Failure
F. C.	67	F	136	1.09	Congen.	Birth	115	58	†	†
S. M.	79	M	153	1.6	Fracture—dislocation	11	78	52	§	†
B. D.	56	F	148	1.3	Polio	10	92	59	§	†
F. F.	53	F	151	1.46	Polio	8	110	54	§	†
J. R.	31	M	155	1.76	Congen.	Birth	78	49	†	†
N. S.¶	75	F	148	1.48	Senile	65	0	50	#	0
H. M.	77	M	160	1.69	Fracture—dislocation	12	28	45	§	0

* The angles of scoliosis and kyphosis were obtained from lateral and anteroposterior chest X-ray film as previously described (1).

† Severe dyspnea at rest.

‡ One or more attacks of heart failure.

§ Dyspnea on mild exertion.

¶ Pulmonary congestion, no clinical evidence of failure at time of studies

Dyspnea on moderate exertion.

carbon dioxide concentrations of expired gas were measured with a Scholander apparatus (8). Duplicate samples from each bag were analyzed and checked within $\pm 0.05\%$. Dead space ventilation was measured by applying the arterial blood and expired gas carbon dioxide tensions to the Bohr equation (9). Measurements of physiologic dead space and alveolar ventilation were corrected for added external dead space volume. Alveolar carbon dioxide tensions were measured with a carbon dioxide meter using end expired (10) and/or rebreathing gas samples (11).

RESULTS

SPIROMETER AND GAS DISTRIBUTION STUDIES

The lung volumes were markedly decreased in six of the seven patients (Table 2). In most of the patients the vital capacity was only slightly larger than the predicted tidal volume of normal subjects. The inspiratory capacities were decreased in all patients except N. S. The maximal expiratory flow rate value ranged from 30 to 110

TABLE 2. Lung Volumes,* Mechanics of Breathing, and Distribution of Inspired Gas

Patient	Inspiratory Capacity (ml)	Expiratory Reserve Volume (ml)	Vital Capacity (ml)	MEFR† (liter/min) Pred. 300-500	MIFR‡ (liter/min) Pred. 300-500	MBC§ (liter/min)	Alveolar Nitrogen %
F. C.	330 (22) #	100 (20)	350 (18)				2.0
B. D.	560 (32)	230 (40)	750 (32)	70	70	35 (59)	2.0
F. F.	695 (39)	100 (16)	750 (31)				
J. R.	520 (19)	100 (11)	620 (17)				
N. S.	1290 (82)	620 (119)	1925 (92)	110	150	25 (36)	1.0, 1.0**
H. M.	980 (40)	180 (25)	1170 (37)	30	100		2.5

* Lung volumes are corrected to body temperature, ambient pressure, and saturated with water vapor (BTPS).

† Maximal expiratory flow rate.

‡ Maximal inspiratory flow rate.

§ Maximal breathing capacity.

|| Concentration of nitrogen in alveolar gas after breathing oxygen for seven minutes (3).

Per cent of predicted value in parentheses (12).

** Single breath test (2).

TABLE 3. Ventilatory Studies

Patient	Inspired Gas	Respiratory Rate (respir/min)	Minute Volume* (liter/min)	Physiological Dead Space* (ml)	Alveolar Min. Vent.* (liter/min)	P _{ACO₂} † (mm Hg)
F. C.	Room air	40	7.1 (4.3)‡			55§
S. M.	Room air	30	12.2 (5.3)	196	3.8	
	99.6% oxygen	22	7.7			
B. D.	Room air	34	9.5 (5.1)			46
F. F.	Room air	14	10.4 (5.7)			
N. S.	Room air	22	9.7 (5.8)			32
H. M.	Room air	31	9.5 (6.6)	96	3.7	44
	99.6% oxygen	31	7.8			
J. R.	Room air, trach. open	23	8.7 (6.8)	75	3.3	55§
	Room air, trach. closed	22	9.1			
	99.6% oxygen	24	7.4			

* Corrected to body temperature, ambient pressure, and saturated with water vapor (BTPS).

† Alveolar carbon dioxide tension, measured with a CO₂ meter using end expired or rebreathing gas samples.

‡ Predicted value in parentheses (12).

§ P_{ACO₂} was not measured on same day as arterial blood studies in Table 4.

liters per minute and the maximal inspiratory flow rates from 70 to 150 liters per minute. There was no evidence of air trapping on the spiograms, i.e., expiration was not prolonged and the sum of the inspiratory capacity and the expiratory reserve volume did not exceed the volume of the vital capacity. The concentration of alveolar nitrogen after seven minutes of breathing pure oxygen was normal. The single breath test was normal in N. S.; all other

patients were unable to perform this test because of their small vital capacities.

VENTILATORY STUDIES

The respiratory minute volumes at rest breathing room air (Table 3) exceeded the predicted values (12). While patients breathed 99.6% oxygen, the minute ventilation decreased in three but was still higher than the predicted value. The increases in minute ventilation were due to

TABLE 4. Arterial Blood Studies

Patient	F _I O ₂ *	Arterial Oxygen Saturation (%)	Dissolved Oxygen† (cm ³ /100 ml)	pH	P _{aco₂} ‡ (mm Hg)
Normal		96-98	>1.5	7.35-7.45	35-45
F. C.	.2093	64		7.29	69
S. M.	.2093	93		7.32	58
	.996	100	.6	7.33	56
F. F.	.2093	94		7.46	45
N. S.	.2093	94		7.45	30
	.996	100	1.8	7.46	30
H. M.	.2093	79		7.40	46
	.996	100	.9	7.37	51
J. R.	.2093	68		7.34	58
	.996	100	.7	7.32	63

* Fractional concentration of oxygen in inspired gas.

† After breathing 99.6% oxygen for 30 minutes.

‡ Arterial carbon dioxide tension.

TABLE 5. Patient J. R. Arterial Blood Gas Studies

Date	F _{IO₂} *	Arterial Oxygen Saturation (%)	Dissolved Oxygen† (cm ³ /100 ml)	pH	Paco ₂ ‡ (mm Hg)
Normal		96-98	>1.5	7.35-7.45	35-45
1/11/60	.2093	61		7.40	67
2/5/60	.2093	62		7.33	63
	.2093§	95			
2/26/60	.2093	87		7.44	44
	.2093§	83		7.54	40
	.996	100	1.4	7.48	41
	.996§	100	.9	7.51	38
8/18/60	.2093 Trach. opened	68		7.34	58
	.2093 Trach. closed	64		7.35	58
	.996	100	.7	7.32	63
	.2093§	86		7.38	53

* Fractional concentration of oxygen in inspired gas.

† After breathing 99.6% oxygen for 30 minutes.

‡ Arterial carbon dioxide tension.

§ Intermittent positive pressure breathing.

increased rates of breathing. The net effect of small tidal volumes and normal physiologic dead spaces resulted in decreased alveolar ventilation in three patients. The end expired alveolar carbon dioxide tension was elevated in four patients and slightly low in one (N. S.).

ARTERIAL BLOOD GAS STUDIES

These measurements were made on six patients at rest breathing room air, and also during ventilation with 99.6% oxygen on four patients (Table 4). The oxygen saturation while breathing room air was low in three patients, ranging from 64% to 79%, and almost normal in three others (S. M., F. F., and N. S.). Breathing 99.6% oxygen, the arterial oxygen saturation was 100%, but in three out of four patients the plasma dissolved oxygen was low, 0.6 to 0.9 vol per 100 ml (normal value > 1.5 vol per 100 ml) indicating a right to left shunt (13). The arterial blood carbon dioxide tension was elevated in all patients except N. S., ranging from 45 to 69 mm Hg. Blood pH values varied between 7.29 and 7.46. Low pH values in the presence of high blood carbon dioxide tension in four pa-

tients indicated an uncompensated respiratory acidosis.

Patients J. R. and N. S. demand special consideration from several points of view. J. R., a 31-year-old white male, was admitted to the Beth Israel Hospital on January 10, 1960, because of severe dyspnea, productive cough, fever, and chest discomfort of three weeks' duration. Prior to this illness, he was able to perform his work as an electrical wirer though with some respiratory difficulty on exertion. Physical examination on admission revealed an acutely ill, cyanotic, drowsy, febrile male in severe respiratory distress. There were faint breath sounds, rhonchi, and wheezes on auscultation of the lungs. A loud pulmonary second sound and a prominent systolic gallop rhythm were observed. The liver was enlarged and tender and there was slight peripheral pitting edema. On the second hospital day the arterial blood oxygen saturation was 61%, arterial blood carbon dioxide tension, 67 mm Hg, and pH 7.40 (Table 5 and Figure 1). Therapy included digitalization, diuretics, bronchodilators, broad spectrum antibiotics, oxygen, and intermittent positive pressure breathing.

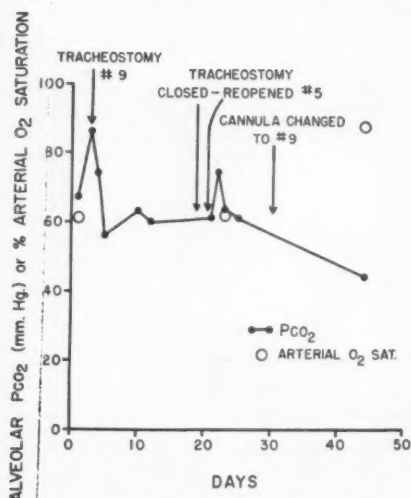


FIGURE 1. Arterial oxygen saturation and alveolar carbon dioxide pressure in patient J. R. during room air breathing.

Despite these measures, his condition deteriorated rapidly. On the third day of hospitalization, temperature was 104° F, the respiratory rate, 60 per minute, heart rate, 160 per minute, and alveolar carbon dioxide pressure, 86 mm Hg. An emergency tracheostomy was performed with dramatic response. Twelve hours later the respiratory rate had slowed to 25 per minute, the heart rate to 100 per minute; the systolic gallop rhythm disappeared, and there was only slight cyanosis while breathing room air. On the fifth hospital day, his sensorium was clear and alveolar carbon dioxide pressure had decreased to 56 mm Hg. After two weeks the tracheostomy was closed, but shortly thereafter dyspnea, disorientation, and the systolic gallop rhythm rapidly returned. A second tracheostomy was performed as an emergency procedure and because of technical difficulties a No. 5 tracheostomy tube was inserted. Although immediate improvement was noted clinically, one day later the arterial oxygen saturation was 62% and the arterial blood carbon dioxide tension was 63 mm Hg. His

behavior varied from confusion and hallucination to relative clarity which correlated roughly with increases and decreases of arterial carbon dioxide pressure. Therefore, the tracheostomy was revised for a larger No. 9 tracheostomy tube. Within a few hours his condition improved markedly, and during the next two weeks the arterial oxygen saturation rose to 87% and the carbon dioxide tension decreased to 44 mm Hg while breathing room air at rest without positive pressure assistance. After breathing 99.6% oxygen for 30 minutes, the arterial oxygen saturation was 100% and the plasma dissolved oxygen 1.4 vol per 100 ml. However, following ventilation with 99.6% oxygen under positive pressure, the plasma dissolved oxygen decreased to 0.9 vol per 100 ml indicating a right to left shunt. After 44 days of hospitalization, the patient was discharged with a No. 9 tracheostomy tube. He was able to return to his regular work. At home, he used an intermittent positive pressure machine (Bird respirator) and suction. After seven months further pulmonary function studies were performed to help determine whether the tracheostomy could be closed. The arterial oxygen saturation at rest while breathing room air through the mouth and the tracheostomy was 68% and the arterial blood carbon dioxide tension was 58 mm Hg. Closure of the tracheostomy resulted in no significant change in either arterial oxygen saturation or carbon dioxide tension. After breathing 99.6% oxygen, arterial oxygen saturation rose to 100%, but plasma dissolved oxygen was only 0.7 vol per 100 ml indicating that right to left shunting had probably increased since the last examination. Arterial P_{O_2} measured with a Clark electrode on an aliquot of the same portion of blood was 250 mm Hg. From these data it was obvious that his condition had deteriorated in spite of his subjective feeling of well-being. It was decided to leave the tracheostomy open and to add antibiotics to his previous treatment to control

bronchial infection. Five months later, the patient had shown marked improvement and was performing full time work.

N. S., a 75-year-old white female, was admitted to the Beth Israel Hospital because of dyspnea of two years' duration. Physical examination revealed a severe degree of kyphosis and signs of congestive heart failure. The chest X-ray examination was inconclusive because of the severe chest deformity. Pulmonary function studies revealed normal lung volumes, increased respiratory rate and minute ventilation, and decreased arterial blood carbon dioxide tension, indicating alveolar hyperventilation. On the basis of these studies, it was concluded that the dyspnea was not due to the severe chest deformity. Treatment was started with digitalis and diuretics and an excellent response was achieved with complete relief of dyspnea.

DISCUSSION

Small lung volumes, increased total minute ventilation, alveolar hypoventilation, hypercapnia, and arterial oxygen unsaturation were found in six of seven patients with kyphoscoliosis. Dead space volumes and distribution of inspired air were normal in all. These findings are similar to other observations (1, 14, 15) in patients with severe kyphoscoliosis. The small lung volumes appear to be related to the severe degree of spinal deformity which diminishes the total volume of the chest and lungs. The rapid respiratory rate and small tidal volumes result in alveolar hypoventilation as relatively large volumes of each respiration are utilized for dead space ventilation (Tables 2-4). Alveolar hypoventilation results in hypercapnia, hypoxemia, and respiratory acidosis (16). In severe cases of kyphoscoliosis, hypoxemia is exaggerated by venous admixture, the arterial oxygen saturation being disproportionately low in relation to the degree of alveolar hypoventilation (Figure 2). Previous observations have indicated that diffusion abnor-

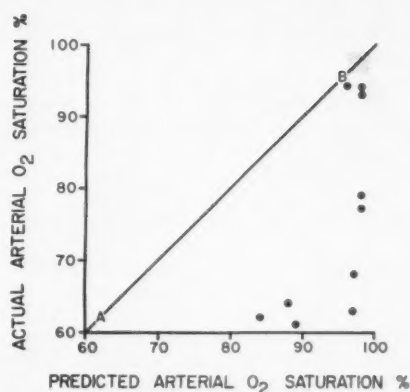


FIGURE 2. Relationship of arterial oxygen saturation to alveolar ventilation during room air breathing. Shaded area depicts normal arterial oxygen saturation. A-B indicates arterial oxygen saturation due to alveolar hypoventilation. Points below this line are due to ventilation-perfusion disturbances, diffusion abnormality, or right to left shunt. Predicted arterial oxygen saturation calculated using alveolar air equation, pH value, and oxy-hemoglobin dissociation curve.

malities are not likely to account for this arterial oxygen unsaturation. In three of four patients studied after ventilation with 99.6% oxygen for 30 minutes, there was 100% arterial oxygen saturation, but the plasma dissolved oxygen was below predicted levels, indicating a right to left shunt. Similar shunting during application of a restrictive corset to the chest of normal subjects has been observed by Caro, Butler, and DuBois (17). In one patient (J. R.) this shunt occurred while breathing 99.6% oxygen under positive pressure, thereby excluding the possibility of venous admixture due to atelectatic lung (18). Though localization of the shunt has not been accomplished in this study, the following speculations can be made concerning its anatomic site. Since pulmonary hypertension frequently develops in severe cases of chest deformity (19), an intracardiac shunt may be produced by reopening the foramen ovale. Another possibility might be related to venous retrograde flow (20), i.e., flow of superior vena caval blood to the pulmonary

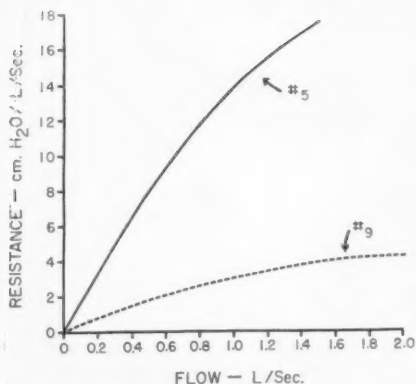


FIGURE 3. Measurement of resistance during varying flow rates through tracheostomy tubes, No. 5 (solid line) and No. 9 (broken line.) At a flow rate of 0.5 liter/sec., the resistance of the No. 5 tube is four times greater than that of the No. 9.

veins through the azygous, mediastinal, and bronchial veins. A third possibility is that the shunt is through pulmonary arteriovenous connections (21, 22).

The use of pulmonary function studies as a diagnostic aid in evaluating dyspnea in patients with severe chest deformity is shown in patient N. S. She had a severe degree of kyphosis and a history of dyspnea of two years' duration. The X-ray examination of the lung was inconclusive. On the other hand the pulmonary function studies did not reveal the characteristic findings previously observed in kyphoscoliotic patients. An excellent response to digitalis and diuretics indicated that dyspnea was probably due to left ventricular failure. This observation indicates that pulmonary function studies can be most helpful in differentiating the cause of dyspnea in patients with severe chest deformity.

Treatment of the acutely ill kyphoscoliotic patient, use of tracheostomy, and long-term management are demonstrated in patient J. R. He was admitted in a moribund state with severe dyspnea. Despite treatment with digitalis, diuretics, antibiotics, oxygen, and intermittent positive

pressure breathing by face mask, his condition deteriorated rapidly. A tracheostomy resulted in increased alveolar ventilation and more effective use of intermittent positive pressure breathing. The closure of the tracheostomy two weeks later resulted in rapid deterioration of his condition. A second emergency tracheostomy was performed and a No. 5 tracheostomy tube inserted. However, his condition improved only after the tracheostomy tube was changed to a No. 9 (Figure 3). Seven months after the second tracheostomy, no improvement was noted in blood gaseous exchange with tracheostomy open when compared with tracheostomy closed (Table 5) during a short period of observation. This finding is similar to observations made by Tyler on patients with tracheostomies (23). Nevertheless, it was felt advisable to retain the tracheostomy or a tracheal window for emergency use during acute respiratory infections. From these data, the following suggestions are made:

1. When a kyphoscoliotic patient reaches the state of cor pulmonale and congestive heart failure, particularly when an acute infection is present, he may no longer respond to usual therapy, including intermittent positive pressure by mouth piece or face mask. A tracheostomy should be performed to increase alveolar ventilation.

2. During the acute stage, the size of the tracheostomy tube (24) is extremely important, i.e., the largest possible tube should be used to reduce resistance to air flow, preferably a No. 8 or No. 9.

3. The main indication for permanent tracheostomy is to eliminate the hazards of emergency tracheostomies during acute respiratory exacerbations (25).

4. The patient can be taught to keep the tracheostomy clean and to sterilize his own catheter. With the aid of suction using a Venturi valve, he can clean his airway even while at work.

5. The use of an intermittent positive pressure machine three to four times a day will increase alveolar ventilation.

6. In permanent tracheostomies, the tracheostomy tube should be changed to a tracheal window in order to eliminate significant increase in the upper airway resistance (26).

SUMMARY

Pulmonary function studies have been carried out in seven patients with severe thoracic deformity. Decreased lung volumes, increased respiratory rates and minute volumes of ventilation, alveolar hypoventilation, hypercapnia, arterial oxygen unsaturation, normal dead space ventilation, and normal distribution of inspired air were observed in six of them. In three of four patients studied after ventilation with 99.6% oxygen for 30 minutes, the arterial oxygen saturation rose to 100%, but the plasma dissolved oxygen was below predicted levels, indicating a right to left shunt.

Failure to respond to usual therapy, including intermittent positive pressure breathing, is demonstrated in the acutely ill kypthoscoliotic patient. The life saving role of tracheostomy in decreasing dead space ventilation, increasing alveolar ventilation, and increasing the effectiveness of intermittent positive pressure is discussed. The use of the largest possible tracheostomy tube is emphasized to reduce resistance to air flow.

The aid of pulmonary function studies in differentiating the cause of dyspnea in patients with severe chest deformity where chest X-ray examinations may be of limited help is suggested.

SUMMARIO IN INTERLINGUA

Studios de function pulmonar esseva executate in sette patientes con sever deformitates thoracic. Esseva constatate, in sex del sette, reduction del volumine pulmonar, acceleration del frequentia respiratori, augmento del volumine de ventilation per minuta, hypoventila-

tion alveolar, hypercapnia, non-saturation oxygenic del sanguine arterial, normal ventilation del spatio morte, e normal distribution del aere inspirate. In tres de quatro patientes studiate post ventilation con 99.6% de oxygeno durante 30 minutas, le saturation oxygenic del sanguine arterial montava a 100%, sed le oxygeno dissolvite in le plasma remaneva infra le predicite nivellos, lo que indica le presentia de un derivation dextero-sinistre.

Non-responsa al therapia usual—incluse intermittente respiration a pression positive—es demonstrate in le acutemente malade patiente cyphoscoliotic. Es discutite le rolo de salva-vita de tracheostomia le qual resulta in un reduction del ventilation del spatio morte, in un augmento del ventilation alveolar, e in un augmentate efficacia de intermittente respiration a pression positive. Es sublineate le desiderato de utilizar le tubo de tracheostomia le plus large possibile pro reducer le resistentia al fluxo de aere.

Es suggerite le possibilitate que studios de function pulmonar es de adjuta in differentiar le causa de dyspnea in patientes con sever deformitates thoracic, i.e. in casos in que roentgenographia thoracic es de utilitate restringite.

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Hereditary Iron-Loading Anemia with Secondary Hemochromatosis

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FIVE CASES MANIFESTING a distinctive form of refractory hypochromic anemia complicated consistently by the later development of hemochromatosis have been studied in an attempt to define further what appears to be a unique clinical entity, one that has been infrequently recognized previously.

Uncomplicated primary, or idiopathic, hemochromatosis only rarely is associated with significant anemia (1). It appears instead to result from an increased intestinal absorptive capacity for dietary iron, this malfunction possibly being inherited and occurring in the absence of anemia or other hematologic abnormalities.

Exogenous hemochromatosis has been described in a variety of patients with longstanding refractory anemias, most often occurring in those who have received multiple blood transfusions (usually more than 100 pints) over long periods (2, 3). However, the histological changes observed in such circumstances are most commonly those of hemosiderosis, in which excessive deposits of iron are demonstrable in the reticulo-endothelial cells but in which there is no evidence of functional or structural disturbance of the parenchymal cells.

Received for publication March 6, 1961.

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This is an abridgment of the thesis submitted by Dr. Byrd to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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The term "secondary hemochromatosis" has been employed to distinguish infrequent cases in which hemochromatosis develops in association with severe prolonged anemia in the absence of the influence of repeated blood transfusions or other measures to account for excessive deposition of iron in the tissues. Anemia per se can stimulate the gastrointestinal absorption of iron (4). In reported cases of anemia and secondary hemochromatosis, the anemia has been described as being hemolytic, aplastic, or refractory in nature (5-8).

The relationships between thalassemia and iron-storage disorders have received considerable comment, including the observation that the deposition of iron in tissue corresponds in some respects to that seen in primary hemochromatosis (9-12). However, multiple transfusions had been administered in many of the cases reported.

Lukl, Wiedermann, and Barbořik (13) described five male members of a Czech family who had chronic hypochromic anemia and associated hemochromatosis, the hematological abnormalities being considered to resemble an "intermediary" form of thalassemia. Pronounced leptocytosis and increased osmotic resistance of the erythrocytes to hypotonic solutions of sodium chloride were constant features. Caroli, Bernard, Bessis, Combrisson, Malassenet, and Breton (14) reported a case in a 39-year-old man with similar morphologic and clinical characteristics, including leptocytosis and increased osmotic resistance. This patient's uncle died with "cirrhosis and anemia," but further specific information about his illness was not documented.

TABLE 1. Iron-Loading Anemia with Secondary Hemochromatosis: Clinical Data from Cases in Literature*

Authors	Gelpi and Ende (15)		Goldish and Aufderheide (16)	Mills and Lucia† (17)		Chesner (18)
Age in years ‡	35	39	55	27	28	14
Age anemia discovered	33	37	34	Early childhood	17?	8
Age hemochromatosis diagnosed	33	?	55	27	?	14
Age onset disabling symptoms	33	?	54	27	26?	14
Predominant symptoms						
Fatigability	+	+	+	+	?	+
Abdominal pain	+	—	+	+	?	+
Thrombophlebitis	+	—	—	+	+	+
Congestive cardiac failure	—	—	+	+	?	—
Physical findings						
Increased pigmentation	+	+	+	—	?	—
Hepatomegaly (cm below costal margin)	Greatly enlarged	1	9	Palpable?	?	3
Splenomegaly (cm below costal margin)	6	—	4	3	?	3
Ankle ulcer	—	—	—	—	?	—
Impaired nutrition and development	—	—	—	—	?	+
Splenectomy	+	—	—	+	+	+
Family history of anemia	+	+	—	+	+	—
Age at death	—	—	55	27	28	14
Treatment						
Transfusions (number of 500 ml units)	14	—	7	Numerous	Many	>6
Iron (oral)	+	—	+	+	?	+
Vitamin B ₁₂	+	+	+	—	?	—
Liver	+	+	+	+	?	+
Folic acid	—	—	+	—	?	—
Pyridoxine	+	—	—	—	?	—
Phlebotomies	—	—	—	—	?	—
Adrenal steroids	+	—	—	—	—	—

* + = Present or yes; — = absent or no; ? = not stated in article or not entirely clear.

† These two patients were brothers.

‡ All six patients were white males.

Despite the observations already noted, the development of clinically significant hemochromatosis as a complication of chronic anemia remains decidedly uncommon. This is possibly explained by the relatively short life expectancy imposed by most disturbances which result in severe refractory anemia.

In the present group of patients studied and in a small number of similar patients

previously described by others, certain clinical and laboratory characteristics appeared to be diagnostically distinctive. These included (1) a history of an anemia that was usually of several years' standing, sometimes dating from childhood; (2) slowly progressive disability or death with clinically significant hemochromatosis at a relatively young age; (3) definitive characteristics of the anemia, including aniso-

chromasia in the presence of hyperferri-
cemia, a striking plethora of siderocytes in
the peripheral blood after splenectomy,
and normal hemoglobin as studied electro-

phoretically; (4) prior administration of
blood transfusions in a quantity well short
of that believed to be required as a signifi-
cant factor in the development of an iron-

TABLE 2. Iron-Loading Anemia with Secondary Hemochromatosis: Laboratory Data
from Cases in Literature *

Authors	Gelpi and Ende (15)		Goldish and Aufderheide (16)	Mills and Lucia (17)		Chesner (18)
Age in years	35	39	55	27	28	14
Hemoglobin, g/100 ml						
Before splenectomy	9	9.7	8	6.8	8.5	3.9
After splenectomy	8-10.3	N.D.	N.D.	1.8-9	8.5	3.8
Erythrocytes†						
Before splenectomy	4.94	5.3	3.11	2.79	3	2.5
After splenectomy	N.D.	N.D.	N.D.	0.9-3	3	1.75
Platelets per mm ³						
Before splenectomy	162,000	500,000	N.D.	Increased	24,000	350,000
After splenectomy	2,700,000	N.D.	N.D.	1,900,000	N.D.	2,000,000
Leukocytes per mm ³	5,400	11,200	12,250	5,120	15,000	4,000
Reticulocytes (per cent)						
Before splenectomy	0-2	2	4	Normal	0.2	1.2
After splenectomy	0-0.3	N.D.	N.D.	N.D.	0	1.6
Blood smear						
Hypochromasia	+	+	+	+	+	+
Anisocytosis	+	+	+	+	+	?
Poikilocytosis	+	+	+	+	+	?
Scattered macrocytes	-	-	+	-	-	?
Target cells	-	-	+	-	-	?
Microcytosis	-	-	-	+	-	+
Siderocytes after splenec- tomy (per cent)	20-25	N.D.	N.D.	24-67	Many	?
Bone marrow						
Normoblastic reaction of a hyperplastic marrow	+	+	+	+	?	+
Iron granules in normo- blasts	-	-	Excessive hemo- siderin	+	+	?
Hemoglobin electrophoresis	Normal	Normal	N.D.	N.D.	N.D.	N.D.
Serum iron, µg/100 ml	144-295	198	187	N.D.	N.D.	N.D.
Erythrocytic porphyrins‡						
Coproporphyrin	N.D.	N.D.	2.4	N.D.	N.D.	N.D.
Protoporphyrin	N.D.	N.D.	Normal	N.D.	N.D.	N.D.
Erythrocytic survival time, days (Cr ⁵¹)	19 (normal, 25 to 40)	23 (normal, 25 to 40)	N.D.	N.D.	N.D.	N.D.

* + = present; - = absent; N.D. = not done; ? = no information.

† Erythrocytes in millions per mm³ of blood.

‡ Porphyrins in µg per 100 ml of erythrocytes.

TABLE 2—Continued

Authors	Gelpi and Ende (15)		Goldish and Aufderheide (16)	Mills and Lucia (17)		Chesner (18)
	35	39	55	27	28	14
Age in years						
Coombs' test						
Direct	Neg.	Neg.	N.D.	N.D.	N.D.	N.D.
Indirect	Neg.	Neg.	N.D.	N.D.	N.D.	N.D.
Abnormal electrocardiogram	+	—	+	—	—	—
Serum bilirubin, mg/100 ml						
Direct	0.50	Normal	Normal	N.D.	N.D.	N.D.
Total	0.85	N.D.	N.D.	N.D.	0.6	N.D.
Fecal urobilinogen, Ehrlich U/24 hr						
Before splenectomy	337-534	N.D.	78-270	N.D.	N.D.	N.D.
After splenectomy	327-430	N.D.	N.D.	N.D.	N.D.	N.D.
Fasting blood sugar, mg/100 ml (or glucose-tolerance test)	Diabetic GTT	N.D.	308	N.D.	N.D.	N.D.
Liver function tests						
Bromsulfalein (per cent) retention in 45 min	2-5	N.D.	10.9	N.D.	N.D.	N.D.
Thymol turbidity, units	2.75	N.D.	12.3	N.D.	N.D.	N.D.
Erythrocyte fragility, per cent of saline						
Initial hemolysis	0.44	0.42	0.54		0.46	
Complete hemolysis	0.32	0.28	0.27	Normal	0.32	Normal
Liver biopsy (or necropsy) compatible with hemo- chromatosis	+	N.D.	+	+	Hemo- siderosis	+

storage disorder (hemochromatosis); and (5) a familial history of anemia (with rare exceptions).

Those cases in the literature that appeared to fit these criteria are summarized in Tables 1 and 2.

CASE REPORTS

CASE 1

A 34-year-old white man, a truck-line operator of German descent, was first seen at the Mayo Clinic in September, 1954, with the complaint of weakness. The patient had been discovered to be anemic in 1947 at the time of a laparotomy for "adhesions." There was no family history of anemia. After this operation, liver extract and an oral preparation of iron were administered for one year without evidence of hematologic improvement.

Anorexia, nausea, and severe epigastric distress of acute onset had necessitated hospitalization in September, 1950. Generalized icterus was noted. The liver was tender and extended 2 cm below the right costal margin. The value for total serum bilirubin was 1.8 mg per 100 ml, and results of other "liver studies" were said to be normal. A diagnosis of hepatitis was made and spontaneous improvement followed.

The patient had remained subjectively well until March, 1954, when he experienced a five-day episode of dry paroxysmal cough, malaise, and "tightness" in the anterior part of the thorax, with sharp retrosternal pain. Dullness to percussion was noted over the right lung anteriorly, and the liver edge was 3 to 4 cm below the costal margin. The value for hemoglobin was 55%, and a stained smear of peripheral blood revealed anisochromasia, polychromasia, and anisocytosis. Normoblastic hyper-

plasia of the bone marrow was demonstrated. A roentgenogram displayed a small right pleural effusion. The following tests provided results that were negative or within normal limits: leukocyte count, blood urea, serum bilirubin, serum proteins, blood culture, and Paul-Bunnell agglutination test. A diagnosis of acute pericarditis was made, antibiotic therapy was instituted, and symptomatic relief was effected after five days.

Recurrent weakness and fatigue had necessitated rehospitalization nine days later. A diagnosis of hemolytic anemia was made after studies revealed a hemoglobin of 57% in combination with increased reticulocytes and a hyperactive bone marrow. The patient was given 100 mg of cortisone per day, continuing this treatment for two months until overt jaundice developed and the splenic tip became palpable for the first time. Splenectomy was performed in June, 1954; congestion and hemosiderosis were the prominent histological features.

However, evidence of abnormal hemolysis had persisted. The patient was hospitalized twice in August, 1954, because of migrating superficial thrombophlebitis and exacerbation of the retrosternal pain. Electrocardiograms were consistently normal.

After another severe exacerbation of phlebitis, thoracic pain, and fatigue, the patient came to the clinic in September, 1954. At that time, he had received a total of 12 pints of whole blood.

Examination disclosed a sallow, yellowish-brown complexion, with pigmentation of the palmar creases. Evidence of thrombophlebitis of the superficial veins of the left forearm and the right short saphenous vein was noted. The liver was palpable 2 cm below the costal margin.

Hematological studies included the following: volume of packed cells (hematocrit), 35%; hemoglobin, 9.3 g per 100 ml of blood; erythrocytes, 2.17 million per mm³ of blood; platelets, 425,000 per mm³; reticulocytes, 4%; erythrocytic sedimentation rate (Westergren method), 105 mm during the first hour; leukocytes, 7,400 per mm³. The leukocytic differential count was 63% neutrophils, 23% lymphocytes, 12% monocytes, and 2% basophils. A stained smear of peripheral blood showed moderate macrocytosis, poikilocytosis, pronounced hypochromasia, and occasional target cells; many of the erythrocytes contained inclusion bodies that stained positively for iron (Figure 1a). The sternal bone marrow was hypercellular (myeloid:erythroid ratio, 1:9), with severely left-shifted normoblastic erythropoiesis. Much phagocytosis of pig-

ment on the part of the reticuloendothelial cells was noted, and specific iron stains gave strongly positive results. Direct and indirect antihuman globulin tests (Coombs), autohemagglutination tests, and acid-resistance tests all gave negative results. The half-life of erythrocytes tagged with radiochromium (Cr⁵¹) was 15 days, in contrast to a normal of 26 days. Total serum bilirubin ranged from 1.2 to 1.6 mg per 100 ml, the direct-reacting fraction being zero on each occasion. Fecal urobilinogen averaged 292 Ehrlich units per 24 hr over a 96-hr period. Erythrocytic protoporphyrin measured 123 µg per 100 ml of erythrocytes, and the coproporphyrin was 3.9 µg. The level of serum iron ranged from 215 to 285 µg per 100 ml. Further study showed that 17.8% of an oral dose of ferrous iron labeled with radioiron (Fe⁵⁹) apparently was absorbed. The results of liver function tests were as follows: no retention of bromsulfalein at 45 min; cephalin-cholesterol flocculation, negative; thymol turbidity, one unit. The Quick prothrombin time was 21 sec (normal control of 19 sec). Total serum proteins included 4.4 g of albumin and 2 g of globulin per 100 ml. The blood sugar under fasting conditions was 200 mg per 100 ml (normal, 80 to 120 mg). Roentgenologic study of the thorax, gall bladder, and upper part of the gastrointestinal tract showed nothing abnormal. Electrocardiography on admission disclosed slurring of the QRS complex in standard Leads II and III. Needle biopsy of the liver demonstrated changes consistent with hemochromatosis.

Since much of the patient's disability could be related to the hemochromatosis, it was elected to do periodic phlebotomies, despite the moderately severe anemia. Seven phlebotomies of 250 ml each were done over a period extending from October 20 to November 28, 1954. The hemoglobin level during this time never decreased below the admission level of 9.3 g per 100 ml.

Throughout the period of observation, recurring superficial thrombophlebitis of the extremities continued. On October 23, clinical evidence of pulmonary embolism with infarction was apparent, accompanied by compatible changes in the thoracic roentgenogram. Anticoagulant therapy with ethyl biscouacetate (Tromexan) and bishydroxycoumarin (Dicumarol) was followed by substantial improvement and was continued thereafter.

However, severe anterior thoracic pain in association with tachycardia developed on November 27. An electrocardiogram showed nodal tachycardia with the QRS abnormalities as be-

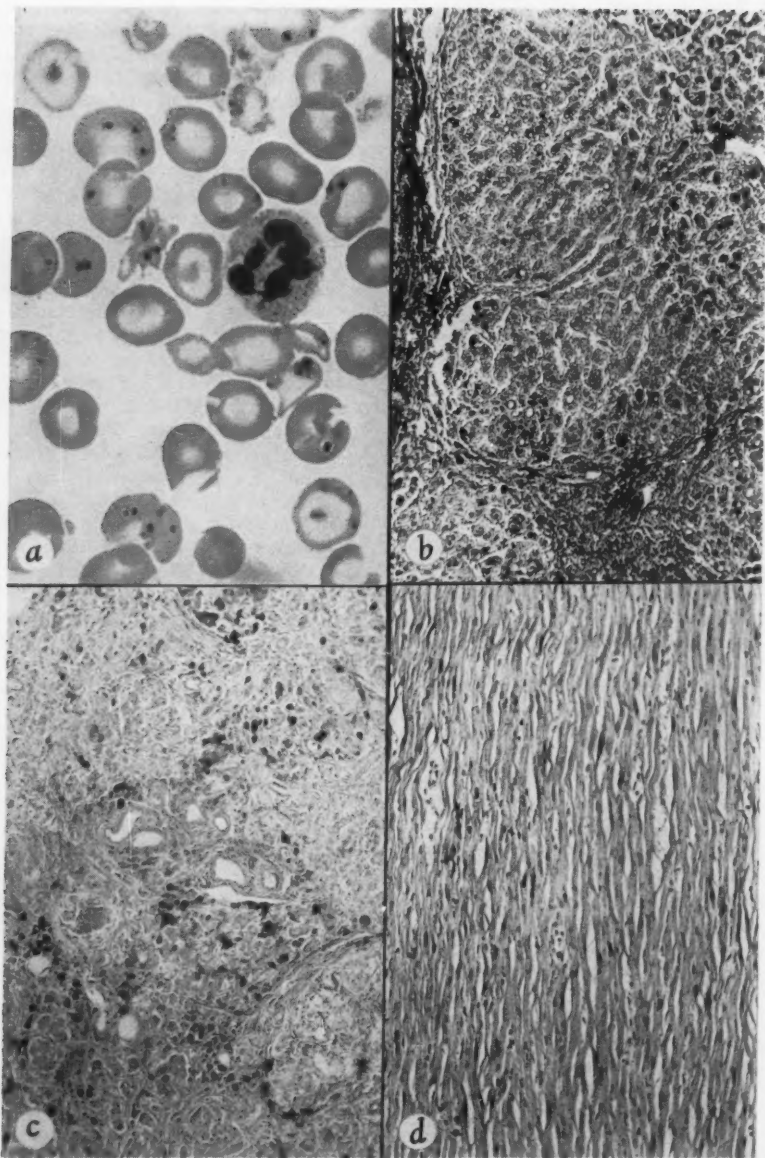


FIGURE 1. Case 1. *a*. Postsplenectomy appearance of peripheral blood. The predominant features include a high percentage of siderocytes and Jolly bodies, hypochromasia, poikilocytosis, occasional target cells, and a distinct tendency to macrocytosis (Wright's stain; $\times 1300$). Smears before splenectomy showed only minor erythrocytic abnormalities and no inclusion bodies. *b*, *c*, and *d*. Sections of liver ($\times 100$), pancreas ($\times 30$), and myocardium ($\times 100$), respectively, showing pigment deposition and tissue fibrosis consistent with hemochromatosis (all H & E).

fore and, in addition, pronounced depression of the S-T segments and inversion of the T waves in thoracic leads V_2 through V_6 . The patient was given quinidine and digitalis, and the arrhythmia disappeared in three days. Subsequent electrocardiograms displayed persistent S-T changes, however. Acute pulmonary edema occurred on December 11; the usual therapeutic measures were unavailing, and the patient died.

Necropsy revealed the following pertinent findings: hemochromatosis, manifested by pigmentation and fibrosis of the liver, pancreas, and lymph nodes (Figure 1b and c); hepatomegaly (2,930 g, normal, 1,800 g); hypertrophy of the heart (400 g, normal, 225 g); diffuse degeneration of the myocardium of the left ventricle, with severe dilatation; mural thrombus of the left auricular appendage; moderate edema of the lungs and bronchopneumonia; thrombosis of the basilar artery, with infarction of the superior surface of the cerebellum in the distribution of the superior cerebellar arteries; minimal arteriosclerosis of the aorta and cerebral arteries. The myocardial changes were thought to be the result of atherosclerosis augmented by "siderotic" fibrosis (Figure 1d).

CASE 2

A 32-year-old manual laborer of Irish descent was admitted to the hospital in December, 1943, with complaints of fatigue and left pleuritic pain. He died one week later.

He had been well until December, 1940, when nervousness, weakness, and cramping left upper abdominal pain had developed. Anemia and hepatosplenomegaly were noted, and iron and vitamins were administered with little apparent effect. No family history of anemia was known at that time. Subsequently, a similar difficulty developed in his younger brother (Case 3).

Weakness and left upper abdominal distress had occurred intermittently, and the patient was hospitalized elsewhere in October, 1941. Hepatosplenomegaly again was noted, the organs extending 4 cm and 3 cm, respectively, below the costal margins. Laboratory values at that time included the following: hemoglobin, 5.4 g per 100 ml; erythrocytes, 2.87 million per mm^3 ; color index, 0.62; reticulocyte count, 0.4%; leukocytes, 7,750 per mm^3 . A differential count showed 44% neutrophils and 56% lymphocytes. Study of blood smears showed abundant platelets, anisocytosis, poikilocytosis, and severely hypochromic erythrocytes.

A diagnosis of Banti's disease had been made, and the spleen was irradiated. No hematological

or clinical improvement followed, and splenectomy was done in November, 1941. The spleen and liver were both enormously enlarged, the right lobe of the liver extending below the iliac crest. The surgeon described the liver as having a cirrhotic appearance. The spleen weighed 2,000 g; microscopic study showed evidence of pronounced chronic congestion. A total of 11 pints of blood was administered during the hospital stay.

Rehospitalization a month later became necessary because of recurrent weakness. The physical findings were unchanged. The hemoglobin level was 7.5 g per 100 ml. Despite the administration of five pints of blood over the next four weeks, the value for hemoglobin was not improved.

During the autumn of 1942, the patient had been able to resume work. In February, 1943, bilateral iliofemoral thrombophlebitis developed. The phlebitis gradually improved but, during November, 1943, progressive weakness and recurrent left pleuritic pain ensued. A productive cough developed, and the patient came to the clinic.

On examination at the clinic, the patient appeared terminally ill, with extreme pallor and sparse body hair. The blood pressure was 120 mm Hg systolic and 44 diastolic, the pulse rate was 120 beats per minute, and the oral temperature was 100.6 F. The nasal mucosa was atrophic, and multiple spider telangiectatic lesions were noted on the thorax. Decreased breath sounds and râles in the base of the left lung were found. The liver was massively enlarged and nodular.

Hematological values were as follows: hemoglobin, 4.7 g per 100 ml; erythrocytes, 2.27 million per mm^3 ; platelets, 580,000 per mm^3 ; leukocytes, 22,000 per mm^3 . The differential count showed 42% neutrophils, 49% lymphocytes, 8% monocytes, and 1% eosinophils. Stained blood smears revealed pronounced macrocytosis, hypochromasia, poikilocytosis, and anisocytosis; many erythrocytes contained inclusion bodies that gave a positive reaction to iron stain (Figure 2a). Other laboratory results were as follows: sedimentation rate, 22 mm per hr; retention of bromsulphalein, 10% in 45 min; blood urea, 60 mg per 100 ml; blood creatinine, 3 mg per 100 ml; carbon dioxide-combining power, 31.5 vol per 100 ml; serum proteins, 7.8 g per 100 ml, with an albumin : globulin ratio of 1.0 : 1.3; serum bilirubin, zero direct and 0.8 mg per 100 ml, total. Grade 2 albuminuria was present. A thoracic roentgenogram showed slight cardiac enlargement,

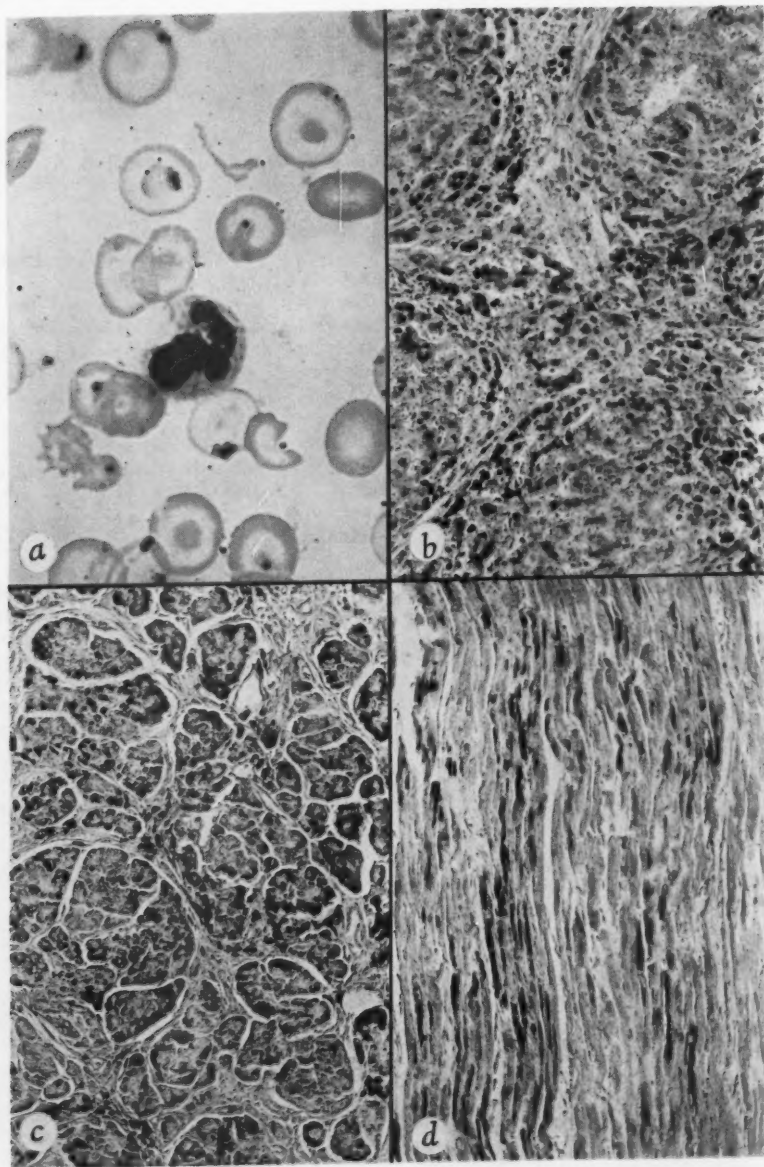


FIGURE 2. Case 2. *a*. Postsplenectomy smear of peripheral blood showing features similar to those in Case 1 (Wright's stain; $\times 1300$). *b*, *c*, and *d*. Sections of liver, pancreas, and myocardium, respectively, demonstrating tissue changes characteristic of hemochromatosis (all H & E; $\times 100$).

with an infiltrative process in the left cardiophrenic angle.

The patient remained in critical condition, forbidding extensive diagnostic studies. Despite supportive measures, including blood transfusions, he died in acute pulmonary edema one week after admission without a specific diagnosis having been established. He had received a total of 27 pints of blood during life.

The following abnormalities were noted at necropsy: hemochromatosis, manifested by pigmentation and fibrosis of the liver, lymph nodes, and pancreas (Figure 2b and c); hepatomegaly (5,277 g, normal, 1,800 g); hypertrophy of the heart (574 g, normal, 373 g) with dilatation of the ventricles; diffuse fibrosis of the myocardium possibly secondary to the siderotic process (Figure 2d); severe pulmonary edema, with beginning bronchopneumonia; esophageal varices; minimal arteriosclerosis of the aorta and coronary arteries; pulmonary embolus, with organization and infarction of the left lower lobe of the lung.

CASE 3*

A 41-year-old cable splicer, the brother of the patient in Case 2, was subjectively well until July, 1956, at which time he experienced the sudden onset of malaise, high fever, pain in the left shoulder, and exertional dyspnea. Examination at that time revealed an acutely ill patient with a blood pressure of 140/0 mm Hg, a pulse rate of 108 beats, and a temperature of 104 F. Moist râles were heard over the base of the left lung, and extension of the liver and spleen beneath the costal margins to a distance of 4 cm and 3 cm, respectively, was noted. Infiltration of the base of the left lung was observed on a thoracic roentgenogram; this process cleared rapidly with antibiotic therapy.

Hematological studies revealed the following: hemoglobin, 5.5 g per 100 ml; erythrocytes, 3.88 million per mm³; differential count, 42% neutrophils, 51% lymphocytes, 1% monocytes, and 6% eosinophils. Stained smears of peripheral blood showed pronounced anisocytosis, poikilocytosis, hypochromasia, polychromasia, and occasional macrocytes. A test of erythrocytic fragility gave normal results. Direct and indirect Coombs' antihuman globulin tests gave normal results. The values for serum bilirubin were 0.2 mg per 100 ml direct and 1.1 mg per 100 ml indirect. The bone marrow showed

* The data in this case were supplied through the courtesy of Dr. James J. Gable, Oklahoma City, Okla.

erythrocytic hyperplasia without specific diagnostic features. Liver function tests gave the following results: no retention of bromsulphalein at 45 min; thymol turbidity, 3.16 units; cephalin-cholesterol flocculation, 2+ in 48 hr. Total serum proteins included 3.9 g of albumin and 2.6 g of globulin per 100 ml of blood. The pattern of a glucose tolerance test was suggestive of mild diabetes mellitus.

The patient was given two transfusions and was discharged with a tentative diagnosis of hemochromatosis. He did well for the next few months except for unusual fatigability and moderate loss of weight. Thereafter, he began to experience night sweats and shortness of breath on exertion, which became so severe he had difficulty carrying out his job. In April, 1957, the appearance of thrombophlebitis in the left short saphenous vein led to his hospitalization.

The results of physical examination were much as before except for the findings associated with the thrombophlebitis and the presence of increased pigmentation in exposed portions of the skin.

The blood and bone marrow findings were essentially unchanged, except that iron-positive granules of pigment were seen in the cells of the erythrocytic series in the bone marrow. The serum iron measured 300 µg per 100 ml. The erythrocytic survival time was shortened as measured by the Cr⁵¹ technique, the patient's cells having a half-life of ten days in contrast to the stated normal of about 40 days. Studies using radioiron showed a half-life disappearance time for iron of 50 min as contrasted to a normal value of about 100 min. The half-life reappearance time was about 15 days as compared to the normal value of four days. Paper electrophoresis of hemoglobin gave a normal pattern. Roentgenological studies showed moderate cardiac enlargement and esophageal changes suggestive of varices. Biopsy of the liver disclosed features of hemochromatosis. The patient was given a trial of pyridoxine therapy, but the anemia did not improve.

CASE 4

A 28-year-old institutional kitchen employee of English and Swedish descent came to the clinic in January, 1955, with complaints of easy fatigability and nonspecific upper abdominal pain.

He had been pallid in early childhood and had developed poorly. Because of anemia, he had received four pints of blood when he was 17 years old. One brother (Case 5 in this study)

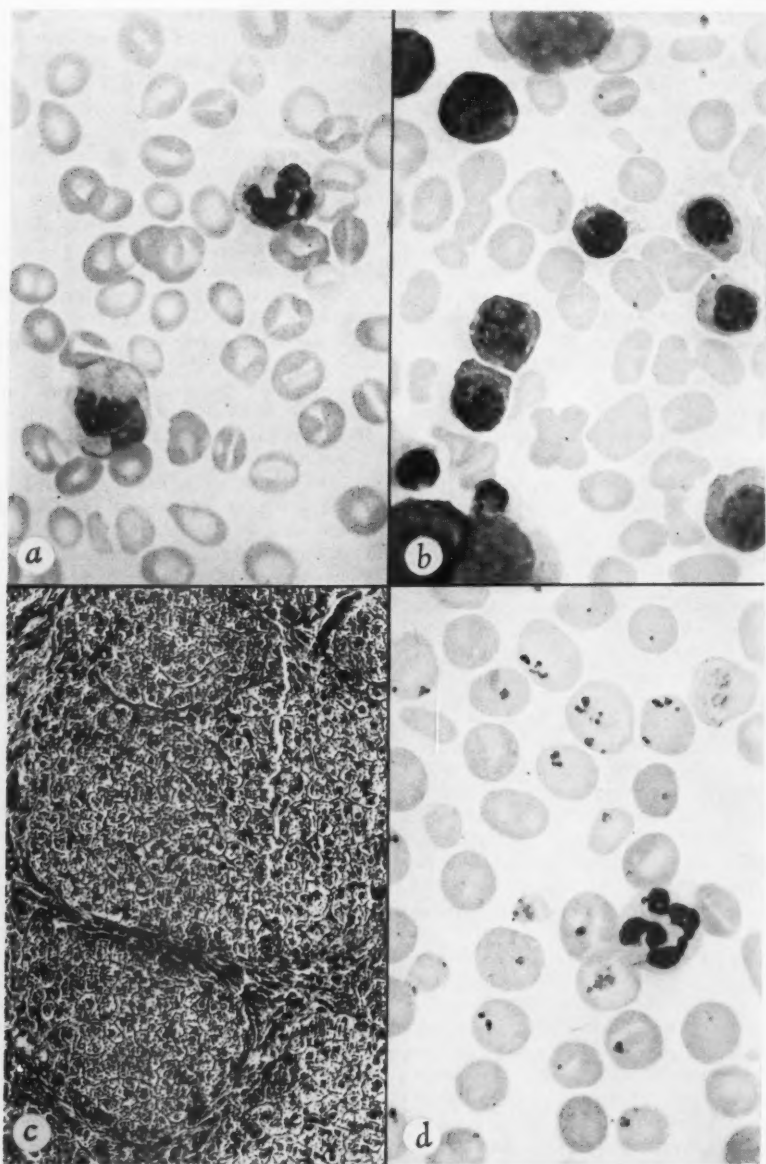


FIGURE 3. Case 4. *a.* Presplenectomy picture of peripheral blood. As in all these cases before splenectomy, anisochromasia and anisopoikilocytosis of only moderate degree may be noted. Leptocytes are rare, and erythrocytic inclusion bodies are absent (Wright's stain; $\times 1000$). *b.* Bone marrow demonstrating normoblastic hyperplasia, an outstanding characteristic in these patients (Wright's stain; $\times 1000$). *c.* Biopsy section of liver showing typical changes of hemochromatosis (H & E; $\times 150$). *d.* Postsplenectomy picture of peripheral blood. The typical striking changes seen in the postsplenectomy state in these patients are demonstrated and may be compared with the presplenectomy findings (Wright's stain; $\times 1000$).

was known to be anemic, and two maternal uncles were said to be "pale" and to have had leg ulcers. Several male first cousins, both maternal and paternal, were said to be "anemic."

Examination at the clinic revealed a Grade 2 systolic precordial murmur that was thought to be hemic in origin, and hepatosplenomegaly to the extent of 3 cm and 1 cm beneath the costal margin, respectively. There was no evidence of pseudoxanthomatosis.

Blood studies revealed the following: erythrocytes, 2.39 million per mm³; hemoglobin, 6.5 g per 100 ml; leukocytes, 6,400 per mm³; platelets, 176,000 per mm³; reticulocytes, 4.8%. A differential count showed 76% neutrophils, 16% lymphocytes, and 8% monocytes. Blood smears showed moderate anisocytosis, poikilocytosis, anisochromasia, occasional macrocytes, and rare target cells (Figure 3a), while the bone marrow revealed a hyperplastic normoblastic picture with hemosiderin in the histiocytes (Figure 3b). Some of the marrow normoblasts contained inclusion bodies that stained positively for iron. The values for serum bilirubin were zero direct and 1.3 mg per 100 ml indirect. Erythrocytic fragility was essentially normal. Electrophoretic studies of the hemoglobin showed 3.5% fetal hemoglobin. The Coombs test gave negative results, and the value for serum iron was 235 μ g per 100 ml. Cholecystography suggested nonfunction of the gall bladder. Electrocardiography showed only minimal non-specific changes in the S-T segments and T waves in the precordial leads. It was thought that the patient had a congenital defect in the synthesis of hemoglobin, with an associated hemolytic component. Splenectomy and cholecystectomy were considered but were deferred.

The patient was seen for follow-up examinations in 1956 and 1957. Similar symptoms were present, but an additional finding on examination at these times was a shallow ulcer on the inner surface of the lower part of the right leg. There was no evidence of venous stasis, and it was thought that this ulcer might be related to the hemolytic anemia. The hematological picture was essentially unchanged. Cr⁵¹ studies showed a moderately shortened erythrocytic life span. Roentgenologic evidence of a duodenal ulcer was obtained on each of these visits; this lesion was thought possibly to be responsible for the complaint of recurrent epigastric pain but was not considered a factor in the perpetuation of the anemia.

In June, 1958, because no significant change in the patient's status was apparent, splenectomy was performed by the patient's home

physician. Sections of the spleen were "consistent with hemolytic anemia," and biopsy of the liver presented the picture of hemochromatosis (Figure 3c). The patient had received 1,500 ml of whole blood before and during the operation.

The patient was seen again at the clinic in February, 1960. He still appeared to be pallid and underdeveloped. The liver was 3 cm beneath the costal margin, and scars of poorly healed superficial ulcers were noted posterior to each medial malleolus. The value for hemoglobin was 9.7 g per 100 ml, the approximate level at which it had been maintained since splenectomy. Leukocytes numbered 12,200 per mm³, platelets 489,000 per mm³, and reticulocytes 9%. The differential count disclosed 66% neutrophils, 15.5% lymphocytes, 17.5% monocytes, and 1% eosinophils. Blood smears now showed generalized hypochromasia, poikilocytosis, macrocytosis, increased platelets, and normoblasts; 38.6% of the erythrocytes contained inclusion bodies that stained positively for iron (Figure 3d). Total serum bilirubin measured 0.72 mg per 100 ml, all of it being indirect. The true blood sugar under fasting conditions was 92 mg per 100 ml (normal, 65 to 90 mg), while the three-hour postprandial true blood sugar measured 124 mg. The patient was feeling less fatigued than in the preoperative period and was able to carry out his duties as a kitchen employee without difficulty.

CASE 5

A 26-year-old forest conservationist, a brother of the patient in Case 4, was first seen at the clinic in December, 1959. He came with the chief complaints of fatigue, dyspnea on exertion, and right upper abdominal pain.

The patient had experienced symptoms of anemia since early childhood and was first hospitalized in 1936 at the age of four years for evaluation of the anemia. At that time, he appeared to be frail and pallid. His liver and spleen were not palpable. The value for hemoglobin was 40%. A definite diagnosis was not made. The patient did not respond to therapy with iron, liver, or beef extract; he was given 125 ml of blood without benefit.

During the following years, he received almost constant oral treatment with iron. At the age of 14, he was given two transfusions, again without lasting benefit.

He was studied extensively elsewhere in April, 1959, because of increased fatigability and inability to carry on with his job in the forests. Transfer records (courteously supplied by the

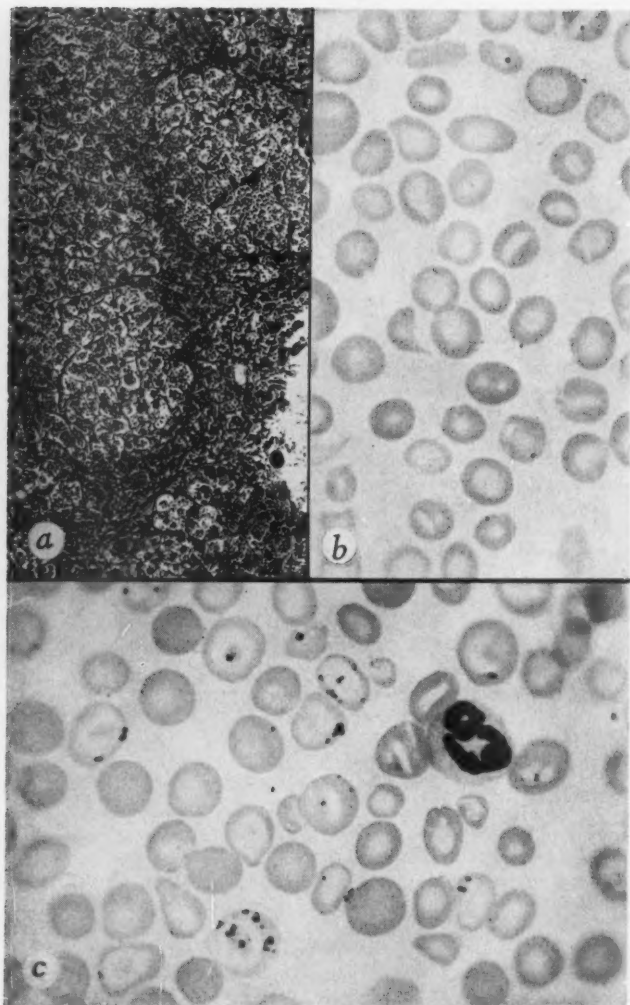


FIGURE 4. Case 5. *a*. Biopsy section of liver showing typical changes of hemochromatosis (H & E; $\times 150$). *b* and *c*. Smears of peripheral blood in presplenectomy and postsplenectomy stages, respectively, demonstrating characteristic abnormalities (both Wright's stain; $\times 1,000$).

University of Michigan Hospital) stated that yellowish linear streaks in the skin of the posterior aspect of the neck were noted; these were considered to be lesions of pseudoxanthoma elasticum. Ophthalmoscopy revealed optic atrophy and angioid streaks. The liver was palpable 11 cm and the spleen 1 cm below the costal margin.

The value for hemoglobin was 6.9 g per 100 ml. Blood smears showed anisocytosis, poikilocytosis, and hypochromasia. The bone marrow was hyperplastic, with prominent normoblastosis, and it exhibited an increased amount of pigment in the reticulum cells. The serum iron was increased to 267 μg per 100 ml, and radioisotope tracer techniques indicated decreased

utilization of iron in the synthesis of hemoglobin and a shortened erythrocytic life span. Liver biopsy was considered diagnostic of hemochromatosis (Figure 4a). The patient was treated with pyridoxine without measurable benefit. He was advised to discontinue oral medication with iron. A single transfusion in November, 1959, was administered for palliation of symptoms.

On examination at the clinic in December, 1959, the positive physical findings were those of a pallid, undernourished, stunted, young adult with hepatosplenomegaly and pseudoxanthoma elasticum. A Grade 2 systolic murmur was noted in the left second and third intercostal spaces in the parasternal region.

Hematologic studies revealed the following: hemoglobin, 6.8 g per 100 ml; erythrocytes, 2.83 million per mm³; leukocytes, 3,900 per mm³; platelets, 116,000 per mm³; reticulocytes, 1.8%. Blood smears showed pronounced anisochromasia and anisocytosis, with occasional macrocytes and poikilocytes (Figure 4b). The serum bilirubin was zero direct and 0.84 mg per 100 ml indirect. No retention of bromsulfalein was present at 45 min. The true blood sugar (fasting) measured 108 mg per 100 ml (normal, 65 to 90 mg), and the serum iron was 232 μ g. The Coombs test gave negative results. Electrophoresis of hemoglobin both by the paper and starch-block methods did not reveal any abnormal hemoglobin. Erythrocytic survival studied by the Cr⁵¹ technique demonstrated an accelerated rate of disappearance of the tagged cells, the value being 3.3% per day compared to a normal of less than 2.5% per day. The total porphyrin concentration was 183 μ g per 100 ml of erythrocytes. An electrocardiogram was abnormal but the changes were nonspecific; a deeply inverted T wave in precordial lead V₃ was noted, and there were deep Q waves in Leads I and aVL and in the precordial Leads V₅ and V₆.

Because of the evidence of significant hemolytic activity, a therapeutic trial with prednisone in a dose of 20 mg per day was carried out. There was no objective or subjective improvement. In February, 1960, splenectomy was performed, preceded by the transfusion of 1,000 ml of whole blood. The spleen was enlarged, weighing 740 g, and the fibrosis and hemosiderosis seen on microscopic examination were consistent with hemochromatosis.

On the seventh postoperative day, left sural thrombophlebitis developed; it responded rapidly to use of anticoagulants. During the two weeks in which the patient was observed after

operation, the hemoglobin increased from 8.1 to 9.1 g per 100 ml. The reticulocyte count was 3.3% 12 days after operation. Postoperative blood smears displayed severe generalized hypochromasia, anisocytosis, and increased poikilocytosis and macrocytosis; in addition, a great number of hypochromic erythrocytes contained inclusion bodies staining positively for iron (Figure 4c). The percentage of these siderocytes increased progressively from 21% on the fourth postoperative day to 37.6% on the thirteenth postoperative day. Further survival studies with Cr⁵¹ showed no appreciable reduction in the accelerated disappearance rate of the erythrocytes.

COMMENT

HISTORY

All of our patients were males, as has been true of all clinically significant cases of anemia of this type with hemochromatosis reported in the literature. Furthermore, the tendency for this condition to occur in families is attested by its occurrence in two sets of brothers in our five patients. Gelpi and Ende (15) noted that the female relatives of two patients whom they studied tended to have anisocytosis and poikilocytosis of the peripheral erythrocytes despite normal hemoglobin values. These observations suggest that the anemia stems from a hereditary fault and is sex-linked, the characteristic being recessive or incompletely recessive in the female. The absence of a history of similar familial disease in Case 1 suggests that disorders of this type may be acquired, although the supposition could not be fortified by a study of the patient's relatives. The delayed clinical expression of the abnormality in three of our cases is also of interest, particularly when it is compared with the early and obvious evidence of anemia and iron-storage abnormalities in thalassemia.

In those cases in which the onset of the anemia apparently was delayed, normal development and subjectively good health had been experienced previously. In these cases, the stigmas of hemochromatosis were

TABLE 3. Iron-Loading Anemia with Secondary Hemochromatosis: Clinical Data in Mayo Clinic Cases*

Case	1	2	3	4	5
Age in years	34	32	41	28	26
Age anemia discovered	27	29	39	Early childhood	4
Age hemochromatosis diagnosed	34	29	39	31	26
Age onset disabling symptoms	30	29	39	23	26
Predominant symptoms					
Fatigability	+	+	+	+	+
Thrombophlebitis	+	+	+	-	+
Abdominal pain	+	+	-	+	+
Congestive cardiac failure	+	+	-	-	-
Physical findings					
Skin changes					
Increased pigmentation	+	-	+	-	-
Pseudoxanthoma elasticum	-	-	-	-	+
Hepatomegaly (cm below costal margin)	2	10	4	3	11
Splenomegaly (cm below costal margin)	1	3	3	1	1
Ankle ulcer	-	-	-	+	-
Impaired nutrition and development	-	-	-	+	+
Splenectomy	+	+	-	+	+
Family history of anemia	-	+	+	+	+
Age at death	34	32	-	-	-
Treatment					
Transfusions (number of 500 ml units)					
Whole blood	12	27	2	7	5½
Packed erythrocytes	0	0	4	0	0
Iron (oral)	+	+	-	+	+
Vitamin B ₁₂	-	-	-	-	-
Liver	+	-	-	-	+
Folic acid	-	-	-	-	-
Pyridoxine	-	-	+	-	+
Phlebotomies	+	-	-	-	-
Adrenal steroids	+	-	-	-	+

* + = Present or yes; - = absent or no.

† All five patients were white males.

present when the patients first appeared for medical evaluation, the underlying anemia by itself apparently having been tolerated fairly well. However, a history of chronic refractory anemia had antedated the appearance of evidence of an iron-storage disorder by many years in all of them.

Fatigability, probably due to the anemia, was the commonest presenting complaint. Later symptoms included upper abdominal pain of a nonspecific aching variety in four of the five cases, developing concurrently

with obvious hepatosplenomegaly. Peripheral thrombophlebitis appeared as a late complication in four of our cases and was consistently observed in those reported elsewhere (14, 16, 17). The pathogenesis of venous thrombosis in this group of patients is obscure. In Case 3, severe recurrent thrombophlebitis developed without splenectomy having been done and in the face of a normal platelet count. However, since these thrombotic complications were observed most consistently after splenectomy,

it is likely that the resultant thrombocytosis is an important pathogenic factor, abetted by the coexistence of progressive debility and anemia.

Congestive cardiac failure was a common problem in patients seen in the terminal stages of the disorder. Nonspecific electrocardiographic abnormalities were noted also in those patients who had no clinically significant cardiac involvement. Cardiac failure developed in one of our patients (Case 2), and he died with acute pulmonary edema; necropsy revealed diffuse myocardial fibrosis and the presence of excessive iron in the myocardial tissues. Although another patient (Case 1) also died with pulmonary edema after the development of angina and intermittent arrhythmia, disease of the coronary arteries, as well as diffuse myocardial fibrosis and iron deposition, was found at necropsy. Such observations tend to confirm the impression that these patients often die from complications of the hemochromatosis and not from the anemia itself.

PHYSICAL FINDINGS

Prominent physical findings in our patients included hepatomegaly, splenomegaly, and cutaneous pigmentation of the hemochromatotic type, with signs of congestive cardiac failure in Cases 1 and 2. Impaired physical development was noted in a set of brothers (Cases 4 and 5); both were poorly nourished and physically stunted, being similar in their general appearance; the diagnosis of "anemia" had been established in early childhood. The changes (skin and ocular fundi) characteristic of pseudoxanthoma elasticum were noted in Case 5.

The clinical findings in our five cases are summarized in Table 3.

LABORATORY FINDINGS

The anemia manifested by these patients was characteristic morphologically. Anisochromia, anisocytosis, poikilocytosis, lepto-

cytosis of mild degree, and occasional macrocytes were features commonly noted in smears of peripheral blood. A striking observation was the appearance of large numbers of erythrocytes with inclusion bodies in the peripheral blood after splenectomy. These particles reacted positively to specific stains for iron; the erythrocytes containing these particles are designated as "siderocytes" (19). As already noted, such cells increased in Case 5 from 21 to 37.6% after splenectomy. Normally, after splenectomy for diseases not involving the erythrocytes, little increase occurs in siderocytes. However, in certain diseases of the erythron, especially the hemolytic and "adynamic" anemias, siderocytes frequently are increased in number to a variable degree after splenectomy (20). The function of the spleen in such cases is not one of destruction of siderocytes but apparently one of "pitting" the excess of iron pigment from the cells, as recently indicated by Crosby's (21) convincing studies. Increased numbers of platelets, the presence of leptocytes, and a tendency to generalized macrocytosis with severe hypochromasia also were prominent changes noted after splenectomy. Similar hematologic aberrations in the postsplenectomy state have been observed previously by others.

The bone marrow picture most usually seen was that of hyperplasia, with normoblastic elements predominating. Sideroblasts were noted in four of our five patients.

The electrophoretic patterns of hemoglobin were normal in the four of our cases thus studied. This absence of any significant abnormalities of the A-2 or fetal hemoglobin fractions further distinguishes this type of anemia from thalassemia and other reported hemoglobinopathies (22, 23).

Tracer studies were utilized in determining the gastrointestinal absorption of iron in Case 1, and normal results were obtained. It would have been of great interest to have studied the iron absorption

TABLE 4. Iron-Loading Anemia with Secondary Hemochromatosis: Laboratory Data in Mayo Clinic Cases*

Case	1	2	3	4	5
Hemoglobin, g/100 ml					
Before splenectomy	8.2	5.4	5.5	6.5	6.8
After splenectomy	9.3	4.7	N.D.	9.7	9.1
Erythrocytes†					
Before splenectomy	N.D.	2.87	3.88	2.39	2.83
After splenectomy	2.17	2.27	N.D.	N.D.	N.D.
Platelets, per mm ³					
Before splenectomy	193,000	Normal	Normal	176,000	116,000
After splenectomy	425,000	580,000	N.D.	489,000	N.D.
Leukocytes, per mm ³					
	7,400	7,750	9,000	6,400	3,900
Reticulocytes, per cent					
Before splenectomy	2.8-8.5	0.4	1.6	4.8	1.8
After splenectomy	15	N.D.	N.D.	9	3.3
Blood smear					
Hypochromasia	+	+	+	+	+
Anisocytosis	+	+	+	+	+
Scattered macrocytes	+	+	+	+	+
Poikilocytosis	+	+	+	+	+
Target cells	+	-	-	+	-
Siderocytes (after splenectomy)	+	+	-	+	+
Bone marrow					
Normoblastic reaction of a hyperplastic marrow	+	N.D.	+	+	+
	(one specimen with only left-shifted erythropoiesis)				
Iron granules in normoblasts	+	N.D.	+	+	Not stained
Hemoglobin electrophoresis					
	Normal	N.D.	Normal	Normal	Normal
Serum iron, µg/100 ml					
	215-285	N.D.	300	235	267-232
Erythrocytic porphyrins‡					
Protoporphyrins	123	N.D.	N.D.	N.D.	183 (total of two types)
Erythrocytic survival (Cr ⁵¹)					
Before splenectomy	N.D.	N.D.	10-day half-life (normal = 40)	Decreased	3.3% destruct./day
After splenectomy	15-day half-life (normal = 26)	N.D.	N.D.	N.D.	2.96% destruct./day (normal = < 2.5%)
Coombs' test					
Direct	Neg.	N.D.	Neg.	Neg.	Neg.
Indirect	Neg.	N.D.	Neg.	N.D.	N.D.

* + = Present; - = absent; N.D. = not done.

† Erythrocytes in millions per mm³ blood.

‡ Porphyrins in µg per 100 ml of erythrocytes.

TABLE 4—Continued

Case	1	2	3	4	5
Serum bilirubin, mg/100 ml					
Direct	0.0	0.0	0.2	0.0	0.0
Indirect	1.2	0.8	1.1	1.3	0.84
Fecal urobilinogen, Ehrlich U/24 hr	292	N.D.	N.D.	N.D.	N.D.
Fasting blood sugar, mg/100 ml	200 (normal = 80-120)	N.D.	Diabetic GTT	124 (3 hr postprandial) (normal = 65-90, fasting)	108 (normal = 65-90)
Abnormal electrocardiogram	+	+	—	+	+
Liver function tests					
Bromsulfalein (per cent) retention in 45 min	0	10	0	N.D.	0
Thymol turbidity, units	1.0	N.D.	3.16	N.D.	N.D.
Cholesterol flocculation	0	N.D.	2+	N.D.	N.D.
Erythrocytic fragility, per cent saline					
Initial hemolysis	0.44	N.D.	0.40	0.44	0.42
Complete hemolysis	0.28	N.D.	0.34	0.32	0.28
Liver biopsy (or necropsy) compatible with hemochromatosis	+	+	+	+	+

pattern at an earlier stage of the disease in our cases. Crosby and Sheehy (24) studied a patient with a similar type of chronic hypochromic anemia and found the rate of iron absorption to be increased. The value for serum iron was increased, ranging from 215 to 300 μg per 100 ml in the four cases in which it was measured. Excessive deposits of iron were demonstrated in the bone marrow and other tissues studied in all our cases.

In all four patients in whom erythrocytic survival was studied, the survival time was shortened, ranging from one-fourth to one-half the normal.

The reticulocyte counts ranged from 0.4% in Case 2 to 15% in Case 1. Values for serum bilirubin were either normal or slightly increased in the indirect fractions.

Studies of erythrocytic coproporphyrin and protoporphyrin were done in two cases and they showed increased values (3.9 and 123 μg per 100 ml of erythrocytes, respectively, in Case 1, and a combined copro-

porphyrin and protoporphyrin value of 183 μg in Case 5). The coproporphyrin : protoporphyrin ratio in the first case suggests that the minor abnormalities are not related to reticulocytosis (25).

Abnormally high values for blood sugar under fasting conditions or a diabetic type of response to the glucose-tolerance test was observed in all four of our patients thus studied; this also is true in most of the cases reported elsewhere in which tissue changes compatible with hemochromatosis are present.

In our cases, the normal fragility of the erythrocytes, the presence of only occasional leptocytes in the presplenectomy picture of peripheral blood, and the increased blood sugar are in contrast to the results in the study by Lukl and co-workers (13) of an "intermediary" form of thalassemia and in the similar case reported by Caroli's group (14).

The laboratory data in our five cases are summarized in Table 4.

PATHOGENESIS

The precise nature of the abnormality in these patients that is responsible for the refractory hypochromic anemia remains obscure. The fact that adequate iron is available is attested by the consistent presence of hyperferricemia, the large numbers of siderocytes in the postsplenectomy state, and the abundant evidence of excessive deposits of iron in various organs and tissues. The increased or adequate quantities of protoporphyrin and coproporphyrin in the erythrocytes appear to rule out a defect in the synthesis of porphyrin as a factor in the pathogenesis of the anemia.

Therefore, it appears reasonable to postulate that the basic and usually hereditary fault is probably enzymatic, the erythrocytes being unable to utilize in a normal manner the readily available iron and porphyrin precursors to form hemoglobin. Furthermore, the erythrocytes present morphologic abnormalities and apparently have a shortened life span. No indication exists of an auto-immune hemolytic disorder, as the results of the Coombs test invariably are negative, and studies designed to demonstrate erythrocytic agglutinins also give normal results.

These patients continue to absorb dietary iron and whatever therapeutic iron may be offered orally, as shown by iron tracer studies. This occurs despite the presence of excessive stores of iron, as emphasized by Goldish and Aufderheide (16), presumably in response to the effects of long-standing anemia and tissue hypoxia. The coexistence of an independent fault in the regulation of the gastrointestinal absorption of iron is also possible.

The ultimate development of clinically significant hemochromatosis may be related reasonably to the effects of steadily increasing deposition of iron. It may be hypothesized that the process is provoked or accelerated by the antecedent and coexisting anemia; however, a concomitant, primary

abnormality in the regulation of the gastrointestinal absorption of iron has not been excluded.

TREATMENT

Treatment of the anemia in this disorder thus far has proved ineffective. Splenectomy did not produce sustained benefit in Cases 1 and 2. In Cases 4 and 5, hemoglobin levels 2 to 3 g per 100 ml greater than those before splenectomy were maintained. The functional capacity in Case 4 was improved, but that in Case 5 was not. Erythrocytic survival times were determined before and after splenectomy in Case 5; significant improvement did not occur. In other reported cases (15, 17, 18), a sustained increase in hemoglobin concentration has not been effected by splenectomy. Furthermore, the problems related to the common development of disabling thrombophlebitis after splenectomy tend to negate any advantage resulting from a modest increase in hemoglobin. The faulty metabolism of iron and the abnormal synthesis of hemoglobin appear not to be correctable in the present state of limited understanding.

The improvement that has occurred in a few reported instances of a rare, morphologically similar hypochromic anemia after the administration of pyridoxine (26) or liver extract (27) has not been observed in the patients under discussion, nor have associated findings suggestive of such deficiencies been noted. The futility of treatment with iron-containing compounds and transfusions in all cases studied and reviewed has been established clearly, and such measures should be avoided because of the problems related to hemochromatosis, which may be present already or may be anticipated.

Since secondary hemochromatosis appears to be a major factor in the progressive disability and fatal outcome observed in most of these patients, treatment should be directed toward this aspect of the problem. Definitive therapeutic efforts in

classic hemochromatosis have been observed after multiple periodic phlebotomies in an effort to mobilize and remove the excessive deposits of iron in the tissues (28). In view of the deteriorating situation in Case 1, it was elected to proceed cautiously with phlebotomy despite the coexistence of moderately severe anemia. After seven phlebotomies, the patient's hemoglobin level had not changed significantly, suggesting that an extended program of phlebotomy might be tolerated, with eventual improvement in the abnormalities related to iron storage. The potential value of this approach was suggested by the decline of the serum iron from 285 to 215 μg per 100 ml during the relatively brief period of its employment. For the same reason, use of phlebotomy was recommended in Cases 4 and 5. The observations of Crosby and Sheehy (24) in their patient with a similar type of chronic hypochromic anemia and hepatic hemosiderosis indicate that multiple phlebotomies are tolerated satisfactorily and that objective evidence of amelioration of the coexisting hemosiderosis can be achieved.

SUMMARY AND CONCLUSIONS

A study has been made at the Mayo Clinic on five patients who had a unique type of refractory hypochromic anemia and in whom hemochromatosis subsequently developed. The features in these cases have been compared with those of similar cases previously reported.

The anemia often appears in such cases to be familial and to be sex-linked, the characteristic being recessive or incompletely recessive in the female. In some instances, it apparently occurs *de novo*. The presence of anemia in these cases has been recognized most often in childhood or the early adult years, preceding the evidence of the hemochromatosis, which usually becomes apparent in the third or fourth decade of life. This contrasts with classic

hemochromatosis, in which the peak age of diagnosis is in the sixth decade.

The characteristic presenting complaints are fatigue secondary to the anemia and symptoms related to the hemochromatosis (nonspecific upper abdominal pain and congestive cardiac failure). An interesting feature in many cases is the occurrence of thrombophlebitis, both before and (more commonly) after splenectomy.

The anemia is characterized morphologically by striking anisochromasia, anisocytosis, poikilocytosis, a tendency to macrocytosis, and occasional leptocytes. In the postsplenectomy state, large numbers of hypochromic erythrocytes containing inclusion bodies that stain positively for iron are noted. The bone marrow shows normoblastic hyperplasia. Other laboratory abnormalities include increased values for serum iron and other findings consistent with hemochromatosis.

No treatment of specific value for this form of anemia is known. The use of iron-containing agents, including the transfusion of blood, may be expected to aggravate the problems related to excessive stores of iron in the body. Splenectomy has resulted in minor increases of the hemoglobin levels in occasional cases, but the high incidence of phlebothrombotic complications thereafter makes the further employment of this procedure inadvisable. By the time this entity usually is recognized clinically, the hemochromatosis, not the anemia, presents the more serious problem; therefore, treatment should be directed primarily at the former. Present observations justify the use of repeated phlebotomies. With earlier recognition of the problem and employment of measures minimizing or effectively contending with its iron-loading aspects, the presently poor prognosis of patients with such disorders may be improved.

More extensive studies of the metabolic faults suggested by the evidence thus far accumulated and the hereditary backgrounds of the persons affected are neces-

sary before the superficially common characteristics of the cases discussed herein may be accepted as manifestations of the same basic disorder or disorders.

ACKNOWLEDGMENT

The authors are grateful to Dr. A. H. Baggenstoss, of the Section of Pathologic Anatomy, for his assistance in the tissue studies.

SUMMARY IN INTERLINGUA

Esseva studiate, al Clinica Mayo, cinque patientes qui habeva un typo unic de refractori anemia hypochromic, con le disveloppamento subsequente de hemochromatosis. Le characteristics in iste casos esseva comparate con le characteristics de simile casos previevemente reportate per alteros.

Le anemia in tal casos pare, frequentemente, esser familial e ligate al sexo, con recessivitate del character (o recessivitate incomplete) in le feminina. In certe casos, apparentemente, illo occurre de novo. Le presentia de iste anemia ha essite recognoscite, in le majoritate del casos, durante le pueritia o le precoce annos adulte, ante le manifestation de hemochromatosis que usualmente deveni apparente in le curso del tertie o quarte decennio del vita. Isto contrasta con hemochromatosis classic pro le qual le maximo del incidentia cade in le sexte decennio del vita.

Le characteristic gravamines de presentation es fatiga secundari a anemia e symptomatas relationate al hemochromatosis, i.e. non-specific dolores supero-abdominal e congestive disfallimento cardiac. Un aspecto interessante de multe casos es le occurrentia de thrombophlebitis, tanto ante como etiam—plus communmente—post le splenectomia.

Le anemia es characterisate morphologicamente per frappante anisochromasia, anisocytosis, poikilocytosis, un tendentia macrocytotic, e le presentia occasional de leptocytosis. In le stato post-splenectomic, grande numeros de erythrocytosis hypochromic es notate que continue corpore de inclusion a tincturabilitate positive pro ferro. Le medulla ossee monstra hyperplasia normoblastic. Altere anormalitates laboratorial es augmentate valores pro le ferro del sero e altere constataciones correspondente a hemochromatosis.

Nulle tractamento es cognoscite que esserea de valor specific pro iste forma de anemia. Le uso de agentes a contento de ferro, incluse transfusiones de sanguine, va aggravar le pro-

blemas relationate a excessive thesauros de ferro in le corpore. Splenectomia ha resultate, in certe casos, in minor augmentos del nivellos de hemoglobina, sed le alte incidentia de complicationes phlebothrombotic post iste mesura rende su uso futur pauco recommendabile. Al tempore quando iste entitate es usualmente recognoscite per su manifestationes clinic, il es le hemochromatosis e non le anemia que presenta le plus serie problema. Per consequente le tractamento debe concerner se primarimente con le hemochromatosis. Le presente observationes justifica le uso de repetite phlebotomias. Si le problema poteva esser recognoscite plus precocemente e si mesuras es empleate que combatte e reduce le phenomeno del cagation de ferro, il non pare impossibile que le prognose pro patientes con tal disordines pote esser meliorate.

Es requirite plus extense studios del errores metabolic que es incriminate per le observationes usque nunc disponibile e del antecedentes hereditari del subjectos afficite, ante que le superficialmente commun characteristics del hic discutate casos pote esser acceptate como manifestationes del mesme disordine o disordines basic.

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CASE REPORTS

Pheochromocytoma and Meningioma of the Foramen Magnum

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THE RELATIONSHIP BETWEEN PHEOCHROMOCYTOMA and other tumors of neural origin, particularly neurofibromas, has been emphasized in recent years. The appreciation of such an association may be of diagnostic value. The present communication concerns the appearance of a meningioma in a patient from whom a pheochromocytoma had previously been removed, and may indicate a further link in a group of related tumors.

CASE REPORT

A 58-year-old white male was initially admitted to the Denver Veterans Administration Hospital in July, 1955, complaining of weakness and unsteadiness of the legs and numbness of the hands. He had been well until 1947, when he began to suffer attacks of sweating, headache, vomiting, and postprandial distress and lost 17 pounds of weight. At that time physical examination was normal except for a blood pressure of 200/100 mm Hg and a fine tremor of the outstretched hands. The thyroid was not enlarged. After a period of treatment with Lugol's solution, a partial thyroidectomy was performed in May, 1948. Relief was only temporary, and in 1950 a cholecystectomy was undertaken for similar symptoms; the gall bladder was found to contain more than 300 calculi. However, nausea, abdominal pain, and weight loss persisted. In November, 1950, he had an episode characterized by agitation, a blank stare, excessive sweating, headache, and numbness of the left hand. This prompted a neurological examination, which was normal. However, the blood pressure was 264/112 mm Hg, dropping in ten minutes to 120/80 mm Hg. This finding led to appropriate studies, followed by the successful removal in January, 1951, of a tumor from the left adrenal gland, which histologically proved to be a pheochromocytoma.

In 1953 the patient noted progressive difficulty in the use of the left hand, accompanied by con-

stant paresthesias. Subsequently he noted similar symptoms in the right hand, as well as weakness of the legs and unsteadiness of gait. A presumptive diagnosis of multiple sclerosis was made and hospital study was undertaken. There was, on examination, a horizontal vestibular nystagmus, both to the right and to the left. Both corneal reflexes were diminished, but otherwise the cranial nerves were intact. The posture of the upper limbs was poorly maintained, particularly that of the left, which fell away and showed "piano playing" movements. There was slight, generalized increase in muscle tone, with an elective weakness most prominent in the left arm and leg. All deep tendon reflexes were brisk, and there were bilateral extensor plantar responses. No disturbance of response to pain, touch, or temperature was noted, but there was impairment of position sense and the ability to discriminate two points over the fingers of the left hand. There was bilateral absence of vibration sense up to the clavicles. The physical examination was otherwise normal. The spinal fluid was unremarkable except for a protein of 135 mg per 100 ml.

In view of the known association between pheochromocytoma and other neural tumors, as well as the clear signs of a high cervical lesion, a growth in the region of the foramen magnum was suspected. A pneumomyelogram showed a filling defect in this area and on August 20, 1955, a suboccipital exploration was undertaken. A firm tumor arising from the dura of the foramen magnum was found; this extended between the cerebellum and brain stem on the left and compressed the medulla to the right. Only partial removal proved possible. The postoperative course was stormy, with marked lability of blood pressure and severe postural hypotension, but eventually a good recovery was made and the patient was discharged on October 19, 1955. The excised tumor upon microscopic examination was found to be a meningioma, with fibroblastic and meningotheelial features.

Eight months after the operation the only neurological abnormalities were a coarse, irregular nystagmus on lateral gaze in either direction and marked decrease of vibratory sense up to the clavicles. He did well until March, 1957, when he developed weakness and spasticity of the legs. In February, 1958, he had a shuffling gait, spasticity of both lower extremities, ataxia of the left arm

Received for publication June 21, 1960.

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and leg, and hyperactive deep tendon reflexes throughout. On March 21, 1958, a cervical myelogram showed a large mass at the foramen magnum. Since it was felt that he could not tolerate further surgical procedures, radiotherapy with a tumor dose of 4,500 r was given to the affected area. He improved considerably and 18 months later had no further neurological signs.

DISCUSSION

Difficulties in the early diagnosis of pheochromocytoma are well illustrated by this patient's history. The subsequent neurological picture was in itself very suggestive of a lesion as high as the foramen magnum (1, 2), and correct interpretation of these signs was aided by the knowledge that pheochromocytomas are often found with other neural tumors.

The association between adrenal chromaffin tumors and neurofibromatosis was initially described in 1910 (3) and has since been amply documented (4-21). For some time this excited little interest, perhaps due to the belief that pheochromocytomas were of no clinical significance (6). Eisenberg and Wallerstein (9) in 1932 noted the presence of von Recklinghausen's disease in 9.4% of cases of adrenal medullary tumors, with other series showing an incidence of from 5 to 25% (15, 19, 21, 22). The converse relationship, that of adrenal chromaffin growths in neurofibromatosis, is not well documented, but a rate of 13% is cited in one study (22). Rosenthal and Willis (10) in 1936 pointed out the apparent preponderance of left-sided adrenal tumors. A recent survey by Chapman, Kemp, and Talliaferro (22) has implicated the right gland most frequently. Since only 35 cases have been reported, no valid conclusions may yet be drawn as to right- or left-sided preponderance.

Before the connection with pheochromocytoma was appreciated, other manifestations of von Recklinghausen's disease were known (8, 23). Any of the neural elements may be involved, giving rise to peripheral nerve tumors, sarcomatous degeneration of such tumors, optic nerve gliomas, meningiomas of cranial and spinal regions, ependymomas, and glial tumors of cerebrum and cord (8, 11, 23-25). Lichtenstein (11) impressively illustrates this point in describing a 39-year-old man who had, in addition to the cutaneous disorder, bilateral acoustic neurinomas, multiple meningiomas of spinal

nerve roots, multiple ependymomas in the spinal cord, a meningioma attached to the inner aspect of the spinal dura mater, an astrocytoma of the cerebellum, hyperplasia of marginal glia of the cord, and focal accumulations of anomalous blood vessels in the dorsal columns of the cord.

Less well-known accompaniments of neurofibromatosis include various vascular tumors of the nervous system, glial tumors of the retina, syringomyelias, and ganglioneuromas (11, 23-25). This list can be expanded, according to Russell and Rubinstein (25) by a group of hamartomatous lesions of the nervous system, including intramedullary schwannomas, meningiomas, angiomas, and glial heterotopias. Meningocele and spina bifida are also encountered, and Russell and Rubinstein (25) have reported the presence of stenosis of the aqueduct by polypoid ependymal granulations with resultant hydrocephalus.

Some authors have associated von Recklinghausen's disease with tuberous sclerosis, the Sturge-Weber syndrome, and von Hippel-Lindau disease in a group to which the terms "neuroectodermal dysplasia" (13) and "neurocutaneous syndrome" (15) have been applied. Russell has challenged this concept, feeling that in the light of existing information it is purely speculative. Despite her criticisms it is difficult both on clinical and theoretical grounds to dismiss the notion of a broad constellation of neuroectodermal disorders. Eventual determination of the true relationships existing in this field will have to await the collection of further data.

Although adrenal chromaffin tumors appear to have a more than casual connection with neurofibromatosis, their status in regard to other ectodermal and neural tumors is not well defined. Glushien, Mansuy, and Littman (15) felt that there was much suggestive evidence to place them in the neurocutaneous syndrome. There are few clinical data to support this contention. Several reports do relate pheochromocytoma to neuroblastoma and ganglioneuromas (26-30) but this is not surprising, since all have a common embryologic origin in the primordial sympathetic cell. There are a few instances in which pheochromocytoma has occurred with von Hippel-Lindau disease (15, 22). One patient has been described who had bilateral

malignant pheochromocytomas and a metastasizing schwannoma of the mediastinum (31). Russell and Rubinstein (25), in discussing this case, take special note of the absence of von Recklinghausen's disease.

The present case is apparently the first recorded instance of a meningioma to be found in a patient with a pheochromocytoma. In addition to neurofibromatosis, von Hippel-Lindau disease, and malignant schwannoma, meningioma can be added to the neural tumors of nonsympathetic origin which have occurred with adrenal medullary growths. This is one of the very few examples where a pheochromocytoma has been seen with a neoplasm of the nervous system in the absence of von Recklinghausen's disease.

Although the combination described may be fortuitous, meningiomas are a frequent accompaniment of neurofibromatosis. Since the latter is related to pheochromocytoma, the association in this case appears significant. It may provide further evidence to justify the concept of the neurocutaneous syndrome and its connection with pheochromocytoma.

SUMMARY

A patient is described who had a meningioma of the foramen magnum two years after surgery for a pheochromocytoma. The well-known association of neurofibromatosis, pheochromocytoma, and other neural tumors is reviewed. The present combination, not heretofore described, is of interest as a possible variant of this group.

SUMMARIO IN INTERLINGUA

Un masculo de 58 annos de etate habeva un pheochromocytoma que esseva excidite a bon successo in 1951. Duo annos plus tarde ille developpava lentamente un quadriparesi spastic, associate con perdita de proprioception ad le nivello del claviculas. Iste constatationes, in association con nostre cognoscentia del relation inter pheochromocytoma e tumores neural, supportava le diagnose e resultava in le ablation de un crescentia al foramine magne que esseva identificate histologicamente como un meningioma. Le frequente occurrentia de neurofibromatosis in patientes con pheochromocytoma es ben cognoscite. Un incidentia de 5 a 25% se trova citate in le literatura. Morbo de von Recklinghausen es frequentemente presente con multe differente tumores del systema nervose, e su frequente connexion con sclerosi tuberosa,

con le syndrome de Sturge-Weber, e con morbo de von Hippel-Lindau ha essite designate como le "syndrome neurocutanee." Etiam pheochromocytoma ha essite incriminate in iste condition, sed pauc evidencia clinic supporta iste conception. Le presente caso es le prime reportate in que un tumor chromaffin adrenal es trovate con un meningioma. Illo es solmente le quarte occurrentia in que pheochromocytoma es reportate in conjunction con un neoplasma de systema nervose in le absentia de neurofibromatosis. Ben que iste casos es possibilemente non plus que fortuite, illos es de interesse e es forsan capace a reinforniar le justification del concepto de un syndrome neurocutanee e de un association de illo con pheochromocytoma.

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Pheochromocytoma with Shock, Marked Leukocytosis, and Unusual Electrocardiograms. Case Report and Review of the Literature

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PHEOCHROMOCYTOMA IS NO LONGER A MEDICAL CURIOSITY when such reviews as that by Watkins in 1957 report over 300 cases (1). However, certain clinical features in the case presented

below have not been commonly noted and seem to be worthy of evaluation.

CASE REPORT

A 53-year-old white female entered the hospital on February 11, 1957, with the chief complaint of a tearing pain in her jaws and gums, associated with profuse sweating, that awakened her at 2:00 AM. The pain initially was steady, but after several

Received for publication June 7, 1960.

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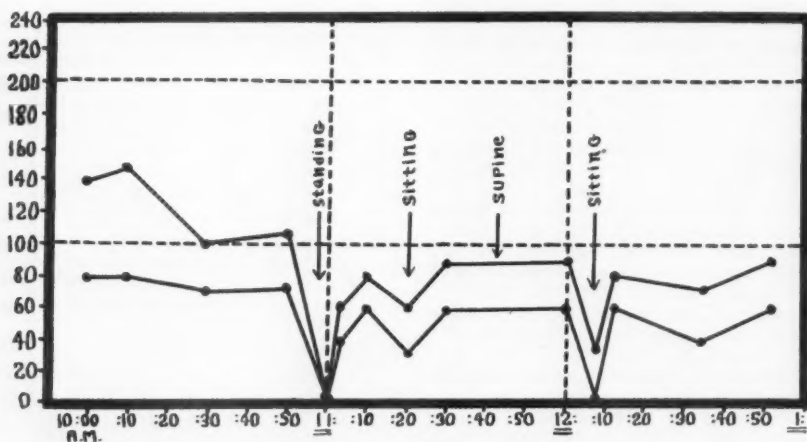
hours became episodic. With each exacerbation there was a simultaneous drenching sweat, occasionally associated with nausea and vomiting. Self-administered aspirin brought no relief. She was admitted to the hospital 12 hours after the onset of symptoms.

Her past health had generally been good. An uneventful appendectomy was performed at age 28. A duodenal ulcer was satisfactorily treated medically at age 38. Two pregnancies were uneventful. Four years prior to the present admission a large uterine fibroid was noted and her blood pressure at that time was 140/90 mm Hg. The systemic review showed only chronic, unchanged constipation and menses as often as every two weeks, on

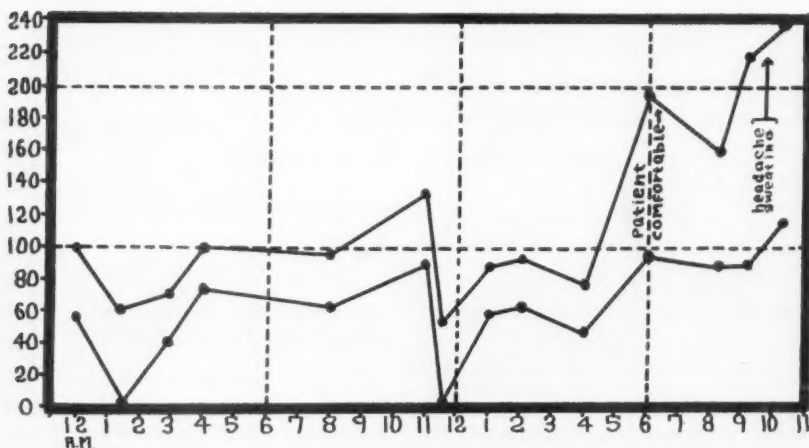
occasion. Family history revealed that an uncle had diabetes.

Physical examination showed a well nourished, well developed white female who was sweating profusely. The blood pressure in the right arm was 180/90 mm Hg, and in the left, 185/95 mm Hg, reclining. The only other positive findings were an irregular pulse of 90, multiple ectopic beats, a split first sound heard at the base of the heart, cold clammy extremities, and a fibroid uterus essentially unchanged from its condition four years previously.

Shortly after admission the pain disappeared but the episodic sweating continued. This sweating was so profound that sheets, blankets, and mattresses



A. Three-hour period on February 13.



B. Twenty-four hour period on February 18.

FIGURE 1. Graphs depicting blood pressure fluctuations.

had to be changed repeatedly every day. The primary problem thereafter was persistent shock of varying degrees. Until the sixth hospital day the blood pressure varied from 90/60 to 170/100 mm Hg except on one occasion. At that time the patient's pulse and blood pressure were unobtainable for 30 seconds when she collapsed while standing up for an X ray. Although the postural effects on the blood pressure became quite obvious, the patient being afraid even to sit up in bed, it was noted that supine blood pressure also remained at hypotensive levels (90/70 mm Hg for three hours after the collapse as noted above) for prolonged periods (Figures 1 A and B).

The temperature varied from 98° to 102.8°F rectally. The pulse fluctuated from 70 to 110/min. Quinidine was required to control the ectopic beats. The quinidine was given intramuscularly every four hours. The patient received 0.6 g on February 11, 1.2 g on February 12, and 0.6 g on February 13, a total dosage of 2.4 g.

On the seventh hospital day intermittent cramping abdominal pain with six liquid stools occurred, along with the start of the menses. On the eighth hospital day an episode of sweating was followed by severe frontal headache and vomiting, and the

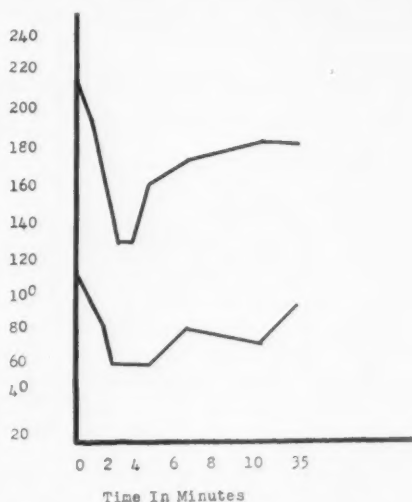


FIGURE 2. Regitine test (5 mg, I.V.), given February 18, 1957.

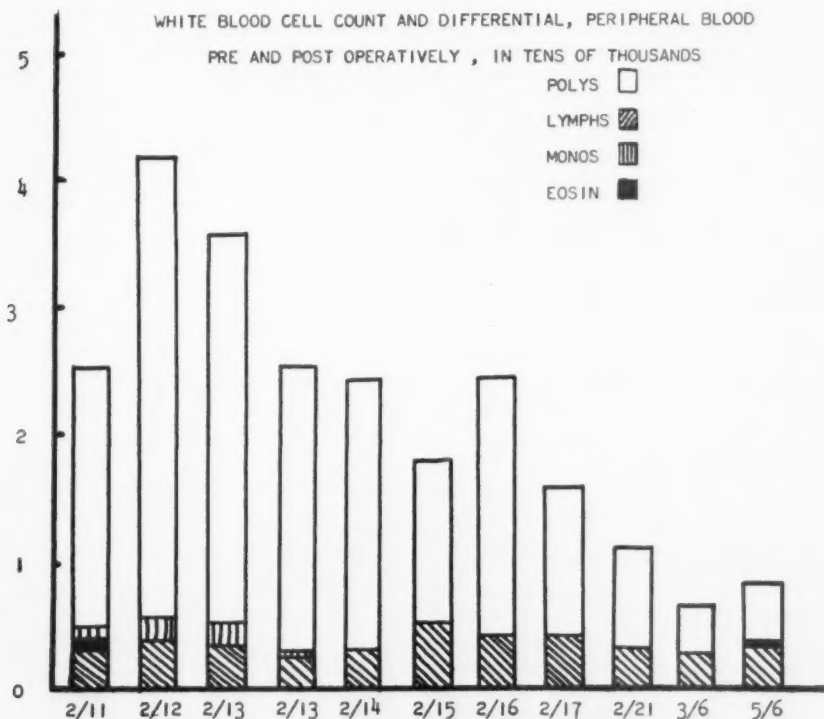


FIGURE 3. White blood counts. Tumor was removed on February 19.



FIGURE 4. Serial electrocardiograms taken pre- and postoperatively. The primary abnormalities are those of prolonged Q-T interval, prominent U waves, depressed S-T segments, and high, peaked T waves.

blood pressure was recorded at 240/115 mm Hg. This was the first truly hypertensive episode despite repeated blood pressure readings during all phases of her attacks. Signs of left ventricular failure developed after this episode and the patient was digitalized. A similar hypertensive episode took place on the following day with blood pressures increasing to 230/120 mm Hg. Regitine tests (2) were performed in the standard manner on both of these occasions and were positive (Figure 2).

From then until surgery on the ninth hospital day the patient's blood pressure was satisfactorily titrated with phenolamine hydrochloride and metaraminol bitartrate.

Other laboratory data obtained preoperatively showed the following: Hb 15.3 g/100 ml; packed cell

volume, 46.5%; corrected erythrocyte sedimentation rate, 25 mm/hr; platelets, 680,000/mm³; serum sodium, 141 to 146 mEq/liter; serum potassium, 3.6 to 4.5 mEq/liter; serum chloride, 98 to 107 mEq/liter; serum bicarbonate, 19 to 23 mmole/liter; fasting blood sugar, 149 and 140 mg/100 ml; blood type, A, Rh-negative; Venereal Disease Research Laboratory test, nonreactive; serum glutamic oxalopyruvic transaminase, 56 units/100 ml. Three blood cultures were negative, as were routine febrile agglutinations. Marked leukocytosis is depicted in Figure 3.

Routine urinalysis disclosed 2+ albuminuria, pH 4.5, and an occasional hyaline cast. Qualitative urine assay for 5-hydroxytryptamine was negative, and urine cultures showed no consistent pathogens. Urinary catecholamines collected in the 24-hour period after the first known hypertensive crisis were markedly elevated with an epinephrine content of more than 300 μ g/24 hr, and norepinephrine content of more than 1,100 μ g/24 hr.

Cerebrospinal fluid chemistry and dynamics were normal; two stool cultures were negative for pathogens. A basal metabolic rate in 1957 was -6%. The patient was too ill prior to surgery to have this repeated.

Appropriate leads from serial electrocardiograms are shown in Figure 4.

Roentgen Findings: Plain film of abdomen on February 12 showed an adynamic ileus (a normal bowel pattern was seen on the following day); chest X ray was normal. Intravenous pyelogram revealed normal kidneys without any evidences of adrenal enlargement. On February 19, perirenal air insufflation with 600 cc of oxygen injected precoccygeally into the right and left sides showed

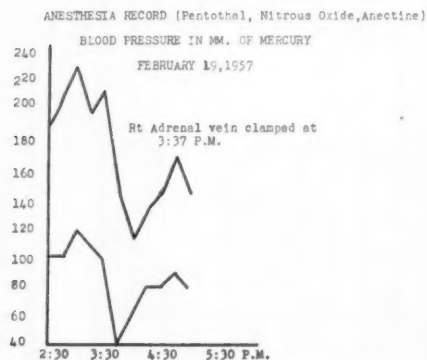


FIGURE 5. Blood pressure fluctuations during surgery.

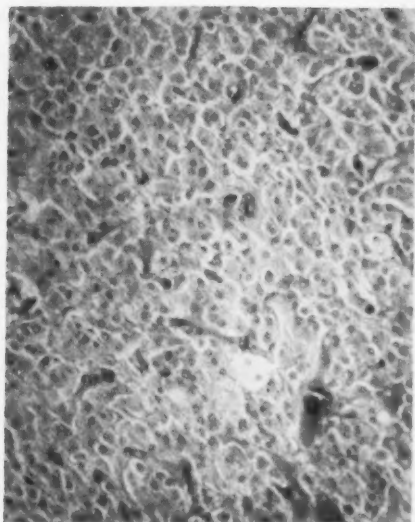


FIGURE 6. Microscopic section of tumor; $\times 160$.

what appeared to be a tumor mass above the right kidney.

The patient was taken to surgery on February 19, the ninth hospital day. Preoperative medication included hydrocortisone. An upper transverse abdominal incision was used; both adrenals and the abdominal cavity were explored. A right adrenal tumor was removed with blood pressure fluctuations as noted in Figure 5. A combination of intravenous Aramine, cortisone, and ephedrine sulfate was used to control the hypotension until the fourth postoperative day, when the situation became stable.

The immediate postoperative course was otherwise uneventful, with the temperature returning to normal on the fourth day. Within two weeks the patient felt well.

She was readmitted to the hospital three months later complaining again of episodes of sweating. Complete studies for recurrent or remaining pheochromocytoma, as well as a general endocrine evaluation, were negative. On the presumption that this phenomenon was then menopausal, estrogen therapy was started, and the patient is asymptomatic at present.

Pathology: The gross tumor measured 5 by 7 by 5 cm. The microscopic picture was benign as seen in Figure 6.

DISCUSSION

There are certain elements of this case which are quite unusual. They include the marked leukocytosis, the persistent shock as the presenting problem, and possibly the electrocardiograms.

It is not the purpose of this report to present a differential diagnosis for either this patient or for pheochromocytomas. However, at least one comment seems to be necessary. As one looks back over the entire course of this patient's illness, certain facets are more obvious than they were when the clinical situation unfolded. The initial blood pressure elevations were of minimal degree. The jaw pain, ectopic beats, sweating associated with pain, episodes of shock, and the electrocardiograms focused attention on the cardiovascular system with the initial diagnosis being myocardial infarction. This again emphasizes the protean nature of adrenal medullary tumor symptomatology.

The leukocytosis was extreme, with 41,500 cells/mm³ being the maximum on the second day. An extensive review of the literature has failed to disclose any reports dealing primarily with white cell abnormalities with pheochromocytomas. Actually, the majority of the literature intimates that the hemogram is usually normal, or no comment at all is made (1-10).

A review of individual or group case reports revealed isolated instances of leukocytosis. Palmer (11) reported a case of sustained hypertension with a white blood count of 11,400/mm³ with 73% polymorphs. Goldenberg, Aronow, Smith, and Faber (12) reported a case with a count of 13,400/mm³, Horn (13) with 14,750/mm³, and Kvale, Minno, and Bennett (14) with 14,800/mm³. Bennett and Mather (15) reported one case with 18,600/mm³ and 76% polymorphs although this patient was 24 weeks pregnant. The highest reports noted were those of Hill and Smith (16) who presented 12 cases, two of which had leukocytosis, one having 20,000 and the other 15,000/mm³, respectively.

The pathophysiology behind this rather extreme leukocytosis is somewhat conjectural. The entire tumor was sectioned and there were no gross evidences of necrosis or hemorrhage to account for the rise. Complete laboratory studies failed to reveal any source of infection. The only explanation is the hormonal effect of epinephrine as described by Wintrobe (17). Epinephrine is reported to cause a leukocytosis in two phases. The first phase immediately follows the injection and involves all of the white cell elements. During the second phase the polymorphs rise again but the lymphocytes

and eosinophiles tend to decrease. If one takes note of Figure 3 it is apparent that the leukocytosis reflected changes primarily in the absolute number of polymorphs and is perhaps consistent with intermittent epinephrine stimulation.

Even if it is granted that leukocytosis of such degree is unusual with a pheochromocytoma, elevated white blood counts in the presence of hypertension of otherwise unknown cause might well suggest adrenal medullary tumor in the differential diagnosis.

The shock as presented in this case was the most perplexing clinical problem. The literature is quite extensive on the subject of postural hypotension and postural tachycardia, stating it to be a common finding in pheochromocytoma (1, 5, 13). The initial situation here, however, was one of almost constant shock aggravated by postural change.

There are only several other cases reported in the literature where preoperative shock was emphasized in the same degree as that manifested here. Gjøl, Dybkaer, and Funder (18) reported a case with shock following hypertensive paroxysms that was so severe that norepinephrine was required to combat each episode. Terry, Tobin, and O'Connor (19) reported on an 18-year-old female who presented initially with a blood pressure of 80/0 mm Hg. Horn (13) also reported a case of paroxysmal hypertensive attacks, induced by eating and changes of position, in which blood pressures varied from 70/50 to 250/140 mm Hg. Here again, however, the episodes of shock were seen to follow an established hypertensive crisis.

Some understanding of the pathophysiology of epinephrine and norepinephrine may clarify this type of clinical situation. An extensive review of the literature on this subject was published by Millar (20).

Epinephrine given intravenously will usually precipitate most of the symptoms of a classical attack. Norepinephrine tends to cause an overall increase in peripheral resistance with elevation of systolic and diastolic blood pressures but with little or no metabolic disturbance. It has been shown in the laboratory that after a prolonged infusion of pressor amines is stopped, hypotension results. It is postulated that compensatory mechanisms overshoot and are responsible for this reactive shock. It is possible

that the shock as presented in this patient indicated just such a physiological situation, perhaps compounded by an adrenal stress-exhaustion phenomenon.

A recent report on the subject of pheochromocytoma with postoperative shock and blood volume studies by Brunjes, Johns, and Crane (21) raises further interesting speculation. Epinephrine and norepinephrine infusions have been found to cause an increased venous hematocrit but a decreased body hematocrit and plasma volume. A chronic hypovolemic state with decreased red cell mass then results which favors the development of shock. Theoretically then, transfusions of whole blood would be helpful in these circumstances.

The electrocardiograms (Figure 4) are unusual and clearly demonstrate reversible changes. In clinical reviews like those of Graham (5) the frequency of the hypertensive pattern and ectopic foci is noted. Watkins (1) comments on acute hyperepinephrinemia followed by marked glucose utilization and gross potassium transfer, which immediately suggests well established electrocardiographic possibilities (22).

The specific relationships between pheochromocytomas and the electrocardiogram have been fairly well documented (23-26). The effect of altered potassium metabolism seems to be most pertinent to the problem at hand. The findings of prolonged Q-T interval, S-T depression, and prominent U waves are common both to hypokalemia and to the case reported, although some degree of coronary insufficiency cannot be ruled out. The positive after-potential noted by Cannon and Sjostrand (23), where the U wave or T wave descends and merges gradually with the P wave without first reaching the baseline, is also seen with hypokalemia and in this patient's cardiograms. The serum potassium in our patient was never markedly depressed when measured. However, the levels at other times or the intracellular content are unknown.

The T waves in the case reported were upright and were the one finding not consistent with the diagnosis of hypokalemia. However, even though the changes caused by norepinephrine are less understood, it does have a marked vagotonic effect which might account for the high, peaked T waves (24).

Bailey (27) has reported quinidine to be a cause of electrocardiographic changes similar to those noted in our patient. However, as seen in Figure 4, the changes were already evident on February 11, 1957, before quinidine was given.

SUMMARY

A case of pheochromocytoma has been presented. The unusual features of marked leukocytosis, persistent shock, and abnormal electrocardiograms have been noted and the pertinent literature reviewed. The white blood count of 41,500/mm³ appears to be the highest recorded at the present time.

SUMMARIO IN INTERLINGUA

Es presentate un caso inusual de pheochromocytoma, insimul con un revista del pertinente litteratura. Un femina de racia blanc de 53 annos de etate, previeamente in bon stato de sanitate, se plangeva initialmente de dolores maxillar e de forte sudoration. Le principal constataciones physic esseva multiple pulsos ectopic ventricular, sudoration periodic, e episodios de prostration e choc, associate con marcate variationes in le tension de sanguine.

Le hypotension postural esseva le plus prominente problema durante le prime septimana del maladia e existeva durante octo dies ante que un typic attacco adreno-medullari esseva observate.

Le positive constataciones laboratorial includeva marcate leucocytose, elevate concentrationes del sucro de sanguine, albuminuria, elevate catecholaminas, positivitate del test a Regitene, e insufflation perirenal de aere (compatibile con le diagnose de un tumor dextero-adrenal. Le electrocardiogramma monstrava un prolongate intervallo Q-T, un depression S-T, prominente undas U, e alte e punctate undas T. Le histopathologia del tumor esseva benigne. Nulle signos macroscopic de hemorrhagia o de necrosis esseva presente.

Le leucocytosis esseva le plus marcate reportate in le litteratura associate con un pheochromocytoma. Le sol explication possibile pareva esser le effecto hormonal de epinephrina super le leucocytos. Le choc e le effectos postural super le tension de sanguine esseva plus extreme que lo que es usualmente incontrate e esseva explicate como reactiones secundari al descarga de epinephrina e norepinephrina ab le tumor. Le possibilitate de un chronic stato hypovolemic (que es a vices associate con pheochromocytomas) esseva etiam considerate como

un factor contributori in le production del choc. Le anomalitates electrocardiographic esseva explicate super le base de hypocaliemia intracellular, le effecto vagotonic de norepinephrina, e le possibilitate de un associate insufficiencia coronari.

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Dextrocardia with Situs Inversus and Atrial Septal Defect Complicated by Acute Rheumatic Fever

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THIS CASE OF A 14-YEAR-OLD GIRL with congenital heart disease is reported because of the following interesting and unusual features:

1. Dextrocardia and situs inversus with associated congenital cardiac anomaly (atrial septal defect), without cyanosis at the present time.

2. Acute rheumatic fever superimposed upon the above, presenting as an acute surgical abdomen and resulting in a left-sided appendectomy.

3. An electrocardiogram showing an upright P wave in Lead I in the presence of a left-sided superior vena cava.

4. The stability of this patient's cardiac status over a period of ten years' observation and in the presence of cardiac enlargement and right ventricular hypertrophy.

CASE REPORT

The patient was first seen in July, 1948, at the age of two and one-half years, and the history

Received for publication March 28, 1960.

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was obtained from her mother. The child was born at term following a normal pregnancy, but was a feeding problem from birth. She had many upper and lower respiratory infections, and was said to be quite irritable. Cyanosis had been noted during crying spells in the first few weeks of life.

The child was small for her age, and weighed 25 pounds. She had slight cyanosis about the eyes and lips; no clubbing of fingers or toes or asymmetry of the chest wall was noted. The apex beat was visible and palpable on the right anterior chest wall, and a systolic thrill was noted in the right third interspace. The rhythm was regular. A Grade 4 rough systolic murmur was present, with maximal intensity in the right third interspace anteriorly; it was transmitted upward toward the neck, and was also heard posteriorly. The liver appeared to be on the left, the stomach bubble on the right.

Fluoroscopy revealed an enlarged, globular heart, with slightly more than one-half of the heart shadow to the right of the midline. The aortic knob was not visualized. The lung fields appeared to be clear, and the hilar shadows were difficult to define because of the size of the heart shadow. Fluoroscopy confirmed the reversed positions of the stomach and liver noted above.

The clinical impression was dextrocardia with situs inversus, probable atrial septal defect, and possibly pulmonic stenosis. The mother was instructed to protect the patient from contact with respiratory infection in others because of the child's history of increased susceptibility to infection, and the increased incidence in such individuals of superimposed rheumatic heart disease.

The patient was next seen at the age of five years. Except for mumps and an occasional sore throat, she had apparently been well. The mother had noted heavy breathing only with severe exertion. At this time the patient weighed 32 pounds and displayed no cyanosis. Physical examination of the heart revealed no changes. Her electrocardiogram was compatible with dextrocardia complicated by right ventricular hypertrophy (Figure 1). Fluoroscopy again showed the abnormal cardiac silhouette noted in the previous examination.

The patient entered school and apparently did well until March, 1959, when she was admitted to St. Peter's Hospital, acutely ill, with the complaint of "pain in the stomach" for the previous five days. This pain was located in the upper abdomen. She developed fever (104 F), a mild sore throat, and a slight cough. Penicillin had been started on the day before admission. The pain increased in severity and gradually shifted to the left lower quadrant.

Physical examination on admission revealed a pale, underdeveloped, thin, white, acutely ill child with a temperature of 101 F. Her pharynx and tonsils were moderately inflamed. The lungs were clear. The heart was enlarged to percussion, with the point of maximal intensity in the right fifth intercostal space at the anterior axillary line. A harsh systolic thrill was palpated over the entire precordium, maximally along the right sternal border. The second heart sound was loudest to the right of the sternum in the second intercostal space, and was distinctly accentuated. The heart sounds at the apex were normal. A Grade 4 harsh systolic murmur was heard over the entire precordium, loudest along the right sternal border in the third intercostal space, and transmitted upward to the base of the heart. No diastolic murmur was heard. The abdomen was diffusely tender and rigid. Tenderness was maximal in the epigastrium and the left lower quadrant, and rebound tenderness was generalized. Liver dullness was percussed on the left; there was tympany on the right over the stomach air bubble. The extremities showed no clubbing, cyanosis, or edema. A surgical consultant concurred in the diagnosis of an acute surgical abdomen with probable appendicitis. Mesenteric adenitis was also considered because of the pharyngitis. White blood count on admission was 13,000/mm³, with 85% polymorphonuclears, including 81% segmented and 4% nonsegmented forms, 11% lymphocytes, and 4% monocytes; hemoglobin, 13 g/100 ml (83%); hematocrit, 40%. Urinalysis showed 2+ albumin, with one to two erythrocytes and three to five leukocytes per high power field. An abdominal laparotomy showed a slightly inflamed appendix on the left side. The mesenteric nodes were enlarged and inflamed. The appendix was removed. The patient's temperature rose to 102 and 103 F for the first five days after the operation. Abdominal pain was diminished, but she continued to be acutely ill. Penicillin and erythromycin were given postoperatively. On the

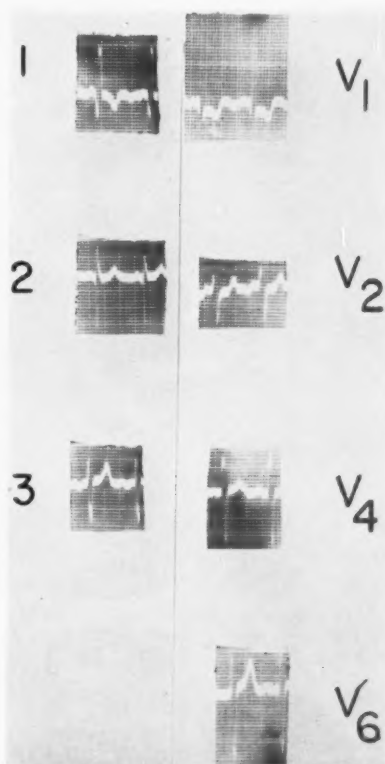


FIGURE 1. Electrocardiogram taken at age of five years (September 13, 1950), interpreted as being compatible with dextrocardia complicated by right ventricular hypertrophy. Note unusual axis deviation in standard leads and low voltage diphasic P-T.

third postoperative day the patient developed signs of consolidation in the right lower lobe, as well as crackling rales compatible with pneumonitis. Tenderness and pain were present over the right Achilles tendon. A roentgenogram of the chest confirmed the diagnosis of bronchopneumonia. Staphylococci were cultured from smears taken from the abdominal cavity during surgery, and beta hemolytic streptococci were grown from a throat smear taken on the fourth postoperative day.

At the end of the first week in the hospital, the patient's temperature was still 102 F; she developed pleuritic pain in the left hemithorax, and a pleural friction rub was heard in the left posterior axillary area. Tenderness and pain were present in the right wrist and later in the right shoulder.

By the ninth hospital day the patient's temperature had dropped to 100 F, and she showed clinical improvement. Sensitivity studies on the beta hemolytic streptococci showed resistance to penicillin.

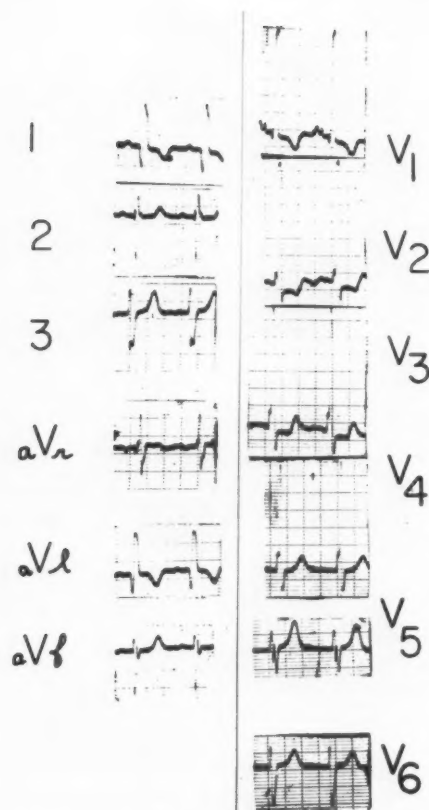


FIGURE 2. Tracing taken during the acute illness March 23, 1959. Note that P-1 is now upright but that otherwise the tracing shows little change in contours.

The sedimentation rate at this time was 115 mm in one hour; antistreptolysin titer, 833 Todd units; C-reactive protein, 4+. The sedimentation rate one week later was 105 mm in one hour; antistreptolysin titer, 1,250 Todd units. Serial electrocardiograms (Figure 2) during the illness showed no significant changes. The child had a low grade fever for the remainder of her hospital stay, with temperatures ranging between 99 and 100 F. All antibiotics and aspirin were discontinued on the thirteenth day, and the patient was signed out against advice on the eighteenth hospital day. A chest roentgenogram before discharge showed clearing of the pneumonitis, marked cardiac enlargement, dextrocardia, and prominent pulmonary vascular shadows, especially in the hilar regions. The roentgenologist commented that right atrial and ventricular enlargement was most prominent.

A week after discharge the patient still had a low grade fever but was entirely asymptomatic. Her sedimentation rate was 116 mm in one hour. She was continued on bed rest at home, and 5 gr of aspirin were prescribed every 4 hr, as well as penicillin, 200,000 units, twice daily by mouth. One month later she was asymptomatic, her sedimentation rate was 49 mm in one hour, and her temperature was normal. Aspirin was stopped, but she was continued on prophylactic oral penicillin. She was followed at monthly intervals for six months, and had no further evidence of rheumatic activity. Her sedimentation rate returned to normal, but her antistreptolysin titer still remained elevated. She returned to school six months after the onset of the acute illness, at which time her cardiac findings showed no significant change.

The patient was readmitted to St. Peter's Hospital on January 5, 1960, for cardiac catheterization.

Physical examination was essentially unchanged. The patient was thin, pale, and underdeveloped for her age, but not acutely ill. Dextrocardia and situs inversus were present. A loud harsh systolic murmur was present over the entire precordium, loudest in the second right intercostal space, with an accompanying thrill. The second heart sound was accentuated in the right parasternal area. Blood pressure was 116/54 mm Hg. An electrocardiogram showed no significant change. The blood count and urinalysis were normal. Cardiac catheterization was performed on January 7, 1960, and the results are shown in Table 1.

A No. 7 catheter was introduced with ease into the left basilic vein and passed into a left-sided superior vena cava, right atrium, and right ventricle. Because of the dextrocardia the catheter was introduced into the left side of the cardiac shadow and passed in reverse to the usual configuration. When the tip of the catheter was at the extreme right side of the ventricular border of the heart shadow, we were unable to advance it any further into the pulmonary artery because of numerous runs of premature ventricular contractions. Pressure in the left-sided right ventricle ranged from 136 to

TABLE 1. Findings During Cardiac Catheterization

Site	Pressure Systolic/Diastolic (Mean) (mm Hg)	Oxygen Saturation (%)
Subclavian vein	—	52.5%
Superior vena cava	—	51%
High right atrium	9 to 19 (13)	79%
Mid right atrium	10 to 20 (13)	82%
Mid right ventricle (outflow)	136/14 (55)	79.8%
Right ventricle (inflow)	153/0 (58)	82.5%
Arterial saturation (ear piece)	—	96%

153 systolic, and zero to 14 diastolic, with a mean of 55 to 58 (Table 1). Oxygen saturations in the right ventricle ranged from 79.8 to 82.5%. The catheter was then withdrawn to the right atrium, where the pressure ranged from 9 to 20 mm Hg, with a mean of 13, and oxygen saturation from 79 to 82%. The right ventricular and atrial pressures were elevated; the oxygen saturations were also above the usual level, but were similar in the right ventricle and atrium. Upon withdrawal of the catheter into the superior vena cava on the left side, the oxygen saturation immediately dropped to 51%. Oxygen saturations by oximetry were repeated several times in each position and were all within 0.5% of the above values. Upon further withdrawal of the catheter to the subclavian vein the oxygen saturation was 52.5%. Dye dilution curves were then done with the catheter in the right ventricle, with the tip at the right border of the heart and also at the left border of the heart, and again in the mid and high right atrium on the left side of the heart, and in the superior vena cava and left subclavian vein. The dye dilution curves in the right atrium, superior vena cava, and subclavian vein indicated the presence of an arterial-to-venous shunt, and also a venous-to-arterial shunt. Arterial oxygen saturation was 96%.

The patient had a moderate number of ventricular premature contractions before the catheterization and displayed marked cardiac irritability during the passage of the catheter. She developed an episode of paroxysmal auricular tachycardia, and was given 2 ml of lanatoside C intravenously. The rhythm reverted to regular sinus tachycardia. She was discharged the following day in good condition.

The findings were compatible with an atrial septal defect with an arterial-venous and veno-arterial shunt (predominantly arterial-venous) in a patient with dextrocardia. Right ventricular hypertension secondary to pulmonary recirculation was suggested by the increased pulmonary vascular markings observed in the chest roentgenograms (Figure 3) in the absence of pulmonary artery catheterization.

COMMENT

Most authors agree that, with mirror-image dextrocardia and situs inversus, the heart is usually normal except for the dextroposition. Campbell and Reynolds (1) state, however, that "at any large clinic for congenital heart disease there are several patients with other congenital malformations added to the dextrocardia and transposition of the viscera." The majority of such patients are cyanotic and have complicated and multiple anomalies. Our patient is unusual in that she has apparently only one associated anomaly—atrial septal defect—and is not cyanotic at this time. Repeated arterial

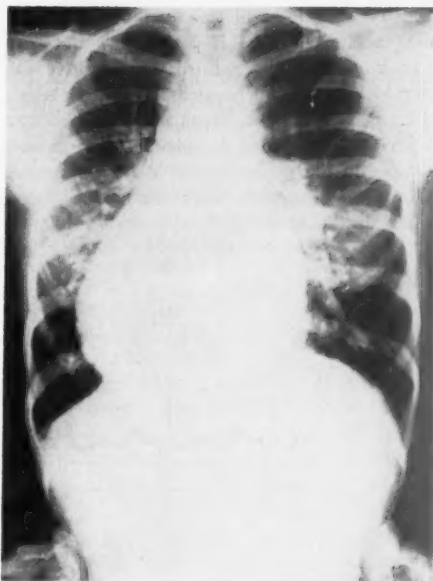


FIGURE 3. Chest X ray taken just prior to catheterization. Note increased pulmonary vascular markings, marked cardiac enlargement, and obvious dextrocardia.

saturation determinations were 96%, and the child shows no clinical cyanosis even after exercise. She was apparently cyanotic in early infancy, and shows some right-to-left shunt on her dye dilution curves at this time, and so must be considered "potentially cyanotic." Her exercise tolerance is remarkably good and has been since she was first observed at the age of two and one-half years. This is in spite of significant cardiac enlargement for more than ten years, as well as electrocardiographic evidence of right ventricular hypertrophy.

Although, according to Taussig (2), 60 to 75% of all persons with atrial septal defects develop acute rheumatic fever, we could find no reference to such a combination in a patient with associated dextrocardia. The latter, however, should have no bearing on it. Acute rheumatic fever presenting as "acute appendicitis" has been reported by Friedberg (3) but, again, our case is unusual in that the appendix was on the left side due to the situs inversus. The presence of the loud murmur obscured any possible cardiac findings of rheumatic fever,

which might have alerted one to the correct diagnosis. Actually, this patient did not show polyarthrititis until the third postoperative day, at which time bronchopneumonia was present. This may have been rheumatic in origin also, especially in light of the pleuritis and consolidation on the opposite side. We were not certain of the diagnosis of rheumatic fever, even when the patient left the hospital, but the accumulation of laboratory data and the sub-

sequent course at home made this diagnosis highly suggestive. The abdominal findings on admission were so dramatic that even in retrospect they could not preclude a laparotomy.

Since auscultation was obscured by the loud murmur of the atrial septal defect, we cannot ascertain whether rheumatic valvulitis was present, or whether there is any residual valvular lesion, particularly mitral insufficiency. Clinically, the patient is as well after her illness as she was before it.

Perhaps the most interesting feature in this case is the electrocardiogram. An upright P wave in Leads 2 and 3 and a left axis deviation are certainly unusual in dextrocardia. There has been surprisingly little change in this patient's electrocardiogram since the age of five years, and the above features have been consistently present. The left axis deviation may be best explained by right ventricular hypertrophy superimposed upon and "canceling" the usual findings of dextrocardia. This can best be demonstrated by viewing the limb leads in a mirror, where a typical right ventricular hypertrophy pattern is seen. This is shown in Figure 4, where the limb leads have been retaken with the arm electrodes purposely reversed to give a "mirror effect." During the course of this tracing four complexes in the reversed Lead I showed an upright P, and thereafter all P waves in this lead were inverted. This probably represents a shifting pacemaker.

Campbell and Reynolds (1) emphasized the relationship between the direction of the P wave in Lead I and the side of the superior vena cava and the venous atrium. They found this to be a constant relationship, in that in all of their nine patients with the superior vena cava on the right, P-I was upright, and in all of their seven patients with this vessel on the left, P-I was inverted. The course of the catheter showed the superior vena cava and venous atrium to be on the left in our patient, even with the upright P wave in Lead I. Bilateral superior venae cavae cannot be ruled out with the present data in our case. This upright P wave may be secondary to hypertrophy of the right atrium, with reversal of the atrial axis deviation in a manner similar to that in the ventricles. Thus this child may originally have had a typical dextrocardia pattern with

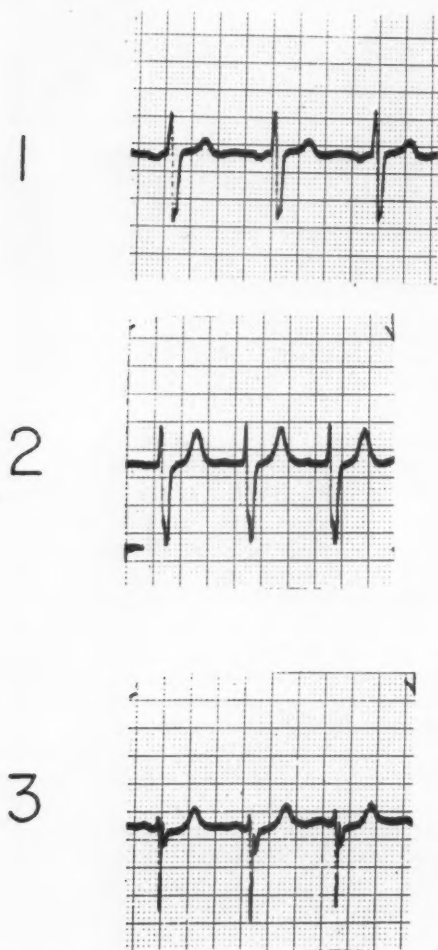


FIGURE 4. Standard leads of an electrocardiogram (March 8, 1960), taken with the arm electrodes purposely reversed to give the mirror effect (see text).

right axis deviation and an inverted P-I, but due to an early development of right atrial and right ventricular hypertrophy the polarity of both ventricles and atria may have reversed. This seems to be likely, since P-I was diphasic and less upright at the age of five years when compared to recent tracings (Figure 1).

This case demonstrates the complicated electrocardiographic findings in dextrocardia, and shows also that the position of the superior vena cava and venous atrium cannot always be determined by the direction of P-I.

SUMMARY

A case of dextrocardia with situs inversus and atrial septal defect who developed acute rheumatic fever is presented. This case had many other interesting features, including unusual findings in the electrocardiogram, lack of cyanosis, and performance of a left-sided appendectomy at the onset of rheumatic fever. Cardiac catheterization data are detailed.

SUMMARIO IN INTERLINGUA

Iste communication reporta le caso de un puera de 14 annos de etate con cognoscite morbo cardiac congenite, investigate per catheterismo dextero-cardiac. Per contrasto con le majoritate de altere casos de dextrocardia associate con sito inverse, le presente caso mon-

strava le associate anormalitate cardiac de defecto atrio-septal. Un altere aspecto de interesse esseva le disveloppamento de acute febre rheumatic que se phesentava como abdomine acute requirente un intervention chirurgic. Un tempestuose curso post-operatori—con bronchopneumonia, pleuritis, febre, e (finalmente) arthralgia—suggereva studios additional que revelava allora le ver natura del morbo acute.

Le constataciones electrocardiographic esseva inusual. Deviation de axe sinistrorse esseva presente, e le typic signos de dextrocardia esseva alterate e obliterate per le configuration de hypertrophia dextero-ventricular. Per contrasto con le situation in previemente reportate casos, un erecte P-I esseva notate in despecto del presentia de un vena cava al sinistra. Es presentate datos detaliate del historia del caso e del resultados del studios de catheterismo. Registrationes illustrative es monstrate.

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Systemic Blastomycosis

Recurrent Neurological Relapse in a Case Treated with Amphotericin B

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DISSEMINATED NORTH AMERICAN BLASTOMYCOSIS is a relatively rare disease, which is generally fatal if untreated. Lesions may occur in the lungs, skin, genitourinary tract, soft tis-

sues, bones, and central nervous system. The causative organism, *Blastomyces dermatitidis*, is highly sensitive to amphotericin B in vitro and in the experimental animal (1-3). Various authors have reported good results in cases of disseminated blastomycosis treated with intravenous amphotericin B (2, 4, 5). In the case reported here, the patient apparently made a good recovery from disseminated blastomycosis following a course of amphotericin B, but sub-

Received for publication March 18, 1960.

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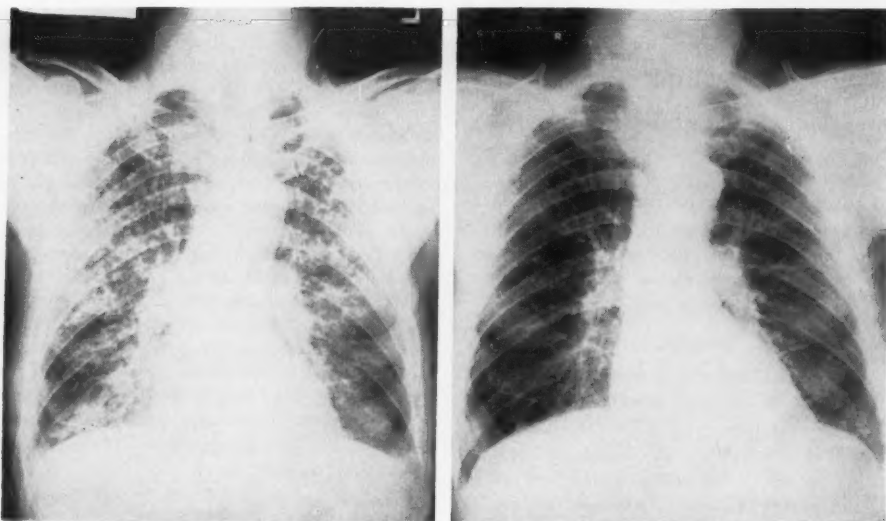


FIGURE 1. A (Left). Chest X ray before treatment. B (Right). Chest X ray four weeks after starting amphotericin B.

sequently suffered two neurological relapses, although no neurological signs or symptoms were present in the original episode of his disease.

Levels of amphotericin B in spinal fluid following intravenous administration are considerably lower than are corresponding blood levels (2, 6, 7), and intrathecal administration of the drug has been used in the treatment of cryptococcal meningitis (2, 7-9). Intrathecal treatment was applied in this case, and was interrupted by the development of paraplegia.

CASE REPORT

A 67-year-old white male was first admitted to the Southeast Kansas Tuberculosis Hospital on June 10, 1958, because of fever of unknown origin and an abnormal chest X ray.

History: The patient had been in good health until May 10, 1958, when he became acutely ill with fever, chills, night sweats, and general weakness, and had to stop working. A week later he developed urgency of micturition and dysuria. On May 20, 1958, he was admitted to the local hospital for investigation, and was found to have prostatic enlargement and urinary infection. His chest X ray showed faint mottling in all lung zones. He received a course of Mandelamine, and the urinary infection and dysuria improved, but the fever persisted. Chest X ray, repeated on May 31, 1958, showed coarse miliary mottling in both lungs (Figure 1A). He had had no more than slight cough and sputum, and the sputum had never been

bloodstained or purulent. He had had no chest pain, but had noted slight dyspnea on exertion for a week or two before transfer to this hospital. He had lost about 20 pounds in weight in the month preceding his admission to this hospital on June 10, 1958.

Apart from a right inguinal hernia, which was repaired in 1954, the patient had had no previous illness of note. No relevant family history was obtained. The patient was born in southeast Kansas, and had spent all of his life in this area. He had worked for 35 years as a coal miner underground. Fifteen years before the onset of this illness he left the mines to work as a clay pipe finisher. This work involved trimming and finishing clay sewer pipes before they were fired, and was not unduly dusty.

Physical Examination: On admission to this hospital the patient was a well-developed, toxic, ill-looking white male who was breathless on moving around in bed and who had a slight cyanotic tinge. Temperature, 100 F; pulse, 80 per min and regular; blood pressure, 110/70 mm Hg. There was no tracheal deviation or enlargement of the cervical lymph nodes. No abnormality was noted on examination of eyes, ears, nose, or throat. His chest was increased in anteroposterior diameter, but the respiratory excursion was good. Percussion note was normal; breath sounds were distant but vesicular in character, and no added sounds were heard. Heart sounds were normal, there was no peripheral edema, and the peripheral arterial pulses were palpable. There was slight tenderness on deep pressure about three inches to the right of the umbilicus, but no muscle guarding. Rectal examination



FIGURE 2. A (Left). Skin lesions at start of treatment. B (Right). Skin lesions after eight weeks' treatment with amphotericin B.

showed moderate enlargement of the prostate, which was spherical and had a very hard consistency. The external genitalia were normal. No neurological abnormality was noted; the knee and ankle jerks were present and equal, and the plantar responses were flexor.

Laboratory Investigations: Sputum specimens were negative on smear and culture for acid-fast bacilli and for fungi. Urine examination showed no albumin or sugar; the urine was loaded with pus cells, and culture of a midstream specimen yielded a coliform bacillus. Blood examination showed a white cell count of 15,700 per mm³ and hemoglobin of 13.1 g per ml. The blood smear showed a polymorphonuclear leukocytosis and hypochromia of the red blood cells. Acid phosphatase, blood urea nitrogen, and liver function tests were all within normal limits.

Chest X ray on admission showed miliary mottling throughout both lung fields, with conglomerate shadows in both midzones. Comparison with films taken on May 22, 1958, and May 31, 1958, showed that the miliary pattern had been present but much less dense on the first of these two films, and that little change had occurred between the second film and the film taken on admission to this hospital. A complete bone survey by X ray was negative. Tuberculin and histoplasmin skin tests were both positive.

Hospital Course: Seven days after admission the patient developed bilateral acute epididymitis, the swelling and pain on the right side developing three or four hours later than that on the left. Treatment with isoniazid and para-aminosalicylic acid (PAS) was started because of the fear that the patient might have miliary tuberculosis, but this treatment had no effect on his fever or on the appearance of his chest X rays. On July 21, 1958,

41 days after admission, the patient developed a papular rash on the face, trunk, and limbs, and these papules grew steadily in size during the ensuing two weeks (Figure 2A). Three days after the rash first appeared a report was received stating that serum taken at the time of admission for complement fixation studies was positive for blastomycosis (1:16), and negative for histoplasmosis and coc-

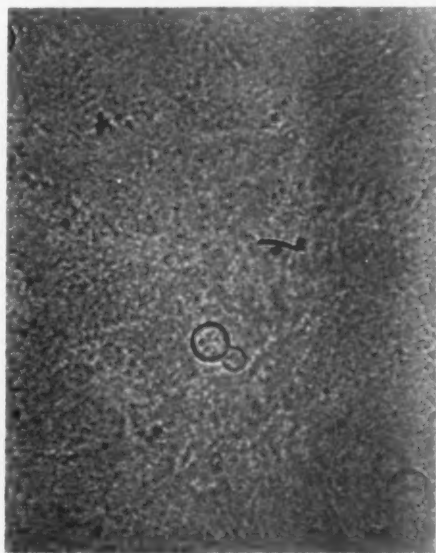


FIGURE 3. Wet smear of pus from skin lesion showing *Blastomyces dermatitidis*. $\times 430$.

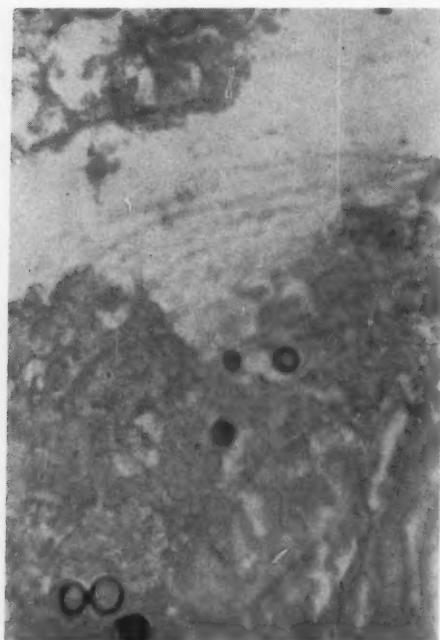


FIGURE 4. Microscopic section of biopsied skin lesion. Grocott's stain, $\times 430$.

cidoidomycosis. A few tiny beads of pus were obtained from one of the skin lesions and smeared on wet preparation. Spherical budding bodies were seen (Figure 3), but sufficient material was not obtained for culture studies. A different skin lesion was biopsied under local anesthesia, and the histological report stated that acute and chronic granulomatous inflammation was present, and that rounded, doubly refractile structures with single budding were seen, compatible with *B. dermatitidis* (Figure 4). A skin test for blastomycosis was done, with negative results.

The patient was accepted for treatment in the cooperative trial of therapy of the deep mycoses (sponsored by the U. S. Public Health Service), and amphotericin B was started on August 11, 1958. Treatment was given daily for three weeks, and on

alternate days for five more weeks. It was given by slow intravenous infusion over a period of six to eight hours, starting with a dose of 0.1 mg/kg body weight, and increasing gradually to the intended dose of 1 mg/kg body weight by the seventh day of treatment. A total dose of 1,594 mg amphotericin B was given in this first course (Table 1). The patient at first responded to the drug with rigors and fever of up to 102.8 F, but his tolerance of the drug increased steadily. After seven days of treatment his skin lesions had improved dramatically and he was feeling better in general. Four weeks after the start of treatment his chest X ray showed marked improvement (Figure 1B); by the end of the eight-week course of treatment, considerable further improvement had taken place, and the X ray showed only slight miliary mottling. By this time the patient felt well generally, and the skin lesions had almost disappeared (Figure 2B). He was seen again by the genitourinary consultant, who stated that the patient's prostate had decreased considerably in size but was still slightly enlarged. The epididymides by this time showed only slight thickening.

Routine testing showed no evidence of drug toxicity to the hepatic, renal, or hematopoietic tissues. Twenty specimens of sputum and gastric lavage were negative on smear and culture for acid-fast bacilli, and these, together with specimens of pus from skin lesions and specimens obtained by prostatic massage, were negative on culture and mouse inoculation for pathogenic fungi. The patient was discharged to his home to continue under outpatient observation on October 11, 1958, at which time he felt well, apart from slight dyspnea on exertion. A serum specimen obtained on October 7, 1958, still showed a titer of 1:64 on complement fixation testing with mycelial phase blastomycin (Table 2).

The patient remained well until October 30, 1958, when he developed symptoms of a head cold, with headache. The head cold cleared up in a few days, but mild headache persisted. On December 15, 1958, he developed fever with chills, and felt weak. On December 20, 1958, he became slightly disoriented, and was readmitted to the hospital on December 23, 1958, for further investigation, 73 days after his discharge.

On examination the patient was acutely ill and confused, with a temperature of 102.4 F. Physical examination showed no abnormality in his chest

TABLE 1. Amphotericin B Treatment Courses

Administration	Period	Duration	Dose
Intravenous	Aug. 11, 1958, to Oct. 5, 1958	8 wk	1,594 mg
Intravenous	Dec. 31, 1958, to Mar. 21, 1959	12 wk	2,473 mg
Intravenous	May 26, 1959, to July 20, 1959	8 wk	1,727 mg
Intrathecal	June 12, 1959, to June 30, 1959	3 wk	6 mg
Total:			5,800 mg

and no localizing neurological signs. Retinoscopy showed slight papilledema. His confusion increased for the few days following admission, and on December 29, 1958, he suddenly developed left facial paralysis and right hemiplegia. He remained conscious but for a short time was unable to speak. There was no neck rigidity and Kernig's sign was absent. The right plantar response was extensor, the left, flexor. Spinal tap was performed and the starting pressure was 240 mm of cerebrospinal fluid. The fluid was clear and colorless and contained 172 lymphocytes per cubic millimeter. Protein was elevated and sugar was reduced (Table 3). Following this spinal tap the patient was able to speak, but was confused and disoriented.

It was felt that the central nervous system lesion was a further manifestation of blastomycosis, but that tuberculous meningitis was also a possibility, and treatment with isoniazid was resumed. Intravenous amphotericin B was also resumed on December 31, 1958, again using an increasing dose, as permitted by the patient's febrile response. On January 5, 1959, the patient was drowsier than formerly, and felt very tired and weak. By this date, all localizing neurological signs had disappeared. On January 7, 1959, during the administration of amphotericin B, he suddenly fell back unresponsive, and became cyanotic, with stertorous breathing. No localizing neurological signs were present. The amphotericin B infusion was replaced by an infusion of hydrocortisone, and in about five hours the patient was considerably better and was

TABLE 2. Serum Complement Fixation Titers with Mycelian Phase Blastomycin

Date	Titer
6/13/58	1:16
7/25/58	0
9/2/58	1:64
10/7/58	1:64
12/4/58	1:16
1/12/59	1:16
2/11/59	0
3/10/59	0
4/3/59	0
5/5/59	0
7/22/59	0
10/15/59	0

talking rationally. Steroids were given with the amphotericin B for the following two weeks, after which the steroids were gradually withdrawn. Intravenous amphotericin B was given daily for four weeks, then on alternate days for a further eight weeks. Spinal fluid findings improved during the course of treatment, and the patient's general condition improved rapidly from January 8, 1959. Chest X rays taken during this hospital stay were all virtually normal, and there was no sign of the former skin rash. Regular examinations of sputum and spinal fluid specimens for fungi by culture

TABLE 3. Spinal Fluid Findings

Date	Protein (mg/ml)	Sugar (mg/ml)	Cells (per mm ³)	Blastomycin Comp. Fix. Test
12/29/58	192	28	172	
1/5/59	308	43	202	Neg.
1/12/59	120	54	178	
1/29/59	88	80	23	
3/4/59	72	81	10	
3/26/59	108	69	35	Neg.
4/21/59	120	77	33	Neg.
5/19/59	272	18	158	Neg.
6/12/59	194	62	75	
6/16/59	200	48	69	
6/20/59	140	—	55	
6/23/59	185	—	22	
6/27/59	250	—	—	
6/30/59	190	71	38	
7/7/59	228	32	41	Neg.
7/21/59	242	65	21	
8/11/59	214	67	—	
8/25/59	175	59	36	
9/15/59	170	75	15	
10/14/59	270	62	15	
11/16/59	125	71	8	
12/14/59	109	67	23	
1/11/60	106	82	28	
3/7/60	84	69	4	

and mouse inoculation were consistently negative. Examinations for acid-fast bacilli were also negative. Complement fixation studies of spinal fluid were consistently negative for fungous antibodies. Urine examination at intervals showed no albumin, sugar, or cells. Liver function tests and blood urea nitrogen values were repeatedly within normal limits. By April 22, 1959, the patient felt well and was discharged to his home once more. The only residual neurological sign was occasional ptosis of the left eyelid when the patient became tired or when he first awakened. Antituberculous drugs were again discontinued at the time of discharge.

The patient remained well until May 13, 1959, when he again complained of headache and weakness and was noted by his wife to be slightly confused. These symptoms increased over the following four days, and he was readmitted to the hospital on May 17, 1959. He had no chest symptoms at this time.

On examination the patient was confused and mildly toxic, with a temperature of 101.6 F. No neurological abnormalities were noted, apart from slight ptosis on the left. There was no remnant of the former skin rash, and no abnormal physical signs relating to the other systems. His chest X ray showed no change from previous films. Spinal fluid again showed lymphocytosis, increased protein, and decreased sugar (Table 3). Between the time of admission and the time of resuming amphotericin B treatment, the patient's condition became worse, with increasing somnolence, confusion, and weakness. By May 26, 1959, he could not stand or walk without assistance. Intravenous amphotericin B treatment was started on May 26, 1959, again with a small dose, which was increased as his febrile reaction to it lessened. Intravenous treatment was given daily from May 26, 1959, until June 8, 1959, after which it was given on alternate days. On this occasion no antituberculous drugs were given. The patient showed a good response to treatment; his confusion disappeared, and his general condition was considerably better by the time the full dose of amphotericin B (1 mg/kg body weight) was reached, five days after the resumption of treatment.

As the patient had apparently had two neurological relapses in spite of intravenous amphotericin B treatment, it was decided to give the drug intrathecally as well, and this mode of administration was started on June 12, 1959. The drug was given intrathecally twice weekly, and intravenously three times weekly. Intrathecal administration was by lumbar puncture: spinal fluid was first removed, 20 mg of the sodium succinate ester of hydrocortisone were instilled through the spinal needle, followed slowly by 1 mg of amphotericin B diluted to 3 ml with spinal fluid. Apart from transient paresthesias and weakness in his legs, no difficulty was encountered with intrathecal treatment until June 30, 1959. On that date he was given his sixth intrathecal injection, without any difficulty being experienced during the proce-

dures. Seven hours later he noted weakness in his legs to the extent that he could not raise them or use them to push himself up in bed. He felt numb, equally on both sides, up to his waist. On examination, sensation of pain and light touch was preserved all over but was diminished from the waist down. Vibratory sense was lost below the iliac crests. Plantar responses were weak but flexor. His legs were flaccid, his knee jerks were weak but symmetrical, and his ankle jerks could not be elicited. Marked symmetrical weakness of all muscle groups below the level of the extensors of the hips was noted. A few hours later he noted that he had no urethral sensation on passing urine, although the sensation of bladder fullness was still present and he had no motor difficulty in initiating micturition. During that night he developed urinary incontinence, which disappeared on the following day.

The paraplegia improved slowly over the ensuing week, and by July 7, 1959, the patient could walk for a few yards without assistance. The numbness in his legs had also improved slightly by this time, and he had no further urinary difficulties. No intrathecal amphotericin B was given after the injection on June 30, 1959. Intravenous administration was continued until the completion of an eight-week course.

The patient was discharged to his home on October 17, 1959. By this time he felt well, and was able to walk one and one-half miles. Numerous sputum and spinal fluid examinations during this admission were negative for acid-fast bacilli and for fungi. Routine hematological examinations, blood urea nitrogen values, and liver function studies were all within normal limits. The patient has been kept under outpatient observation since discharge, and at the most recent examination (March 7, 1960), no loss of muscle power was detected. The left knee jerk was diminished and the right knee jerk was absent. Both ankle jerks were absent, and the plantar responses were flexor. At this time, seven and one-half months after the cessation of treatment, there was no evidence of relapse of blastomycosis.

DISCUSSION

The pathogenesis of North American blastomycosis is poorly understood. It seems likely that the original infection occurs most commonly by way of the respiratory tract (5, 10). This route of infection is suggested by the way in which the present case evolved. An increasing miliary pattern on chest X ray and prostatism were followed by the development of bilateral epididymitis and a papular skin rash. Overt central nervous system involvement followed later, after the other manifestations of disease had apparently responded satisfactorily to treatment with intravenous amphotericin B. The diagnosis of North American blastomycosis

in this patient seems open to little doubt in the case of the skin lesions, but is at present only presumptive as far as the pulmonary, genitourinary, and central nervous system manifestations are concerned. The nature and course of these manifestations and their response to amphotericin B, but not to antituberculous drugs, make the presumptive evidence strong.

Systemic North American blastomycosis appears to respond very well to amphotericin B, which is now the treatment of choice. Seabury and Dascomb (2) report no recurrence in four of their five treated cases, and in the fifth case, a man who died of staphylococcal pneumonia, cultures following autopsy were negative for *B. dermatitidis*. None of these cases had central nervous system disease at any stage. At the time of writing, the only recorded case of proved blastomycosis meningitis successfully treated with amphotericin B is the one reported by Carmody and Tappen (11). Their case responded well to amphotericin B given intravenously over a period of eight weeks, and there had been no recurrence of disease seven months from the cessation of treatment.

Our patient was less fortunate, in that he first showed evidence of central nervous system involvement two months after the end of an eight-week course of intravenous amphotericin B, and that he had a relapse of his central nervous system disease two months after the end of a further 12-week course of intravenous treatment. The neurological signs and symptoms and the spinal fluid abnormalities responded promptly to intravenous treatment, but the infection apparently persisted. Seabury and Dascomb (2) suggest, from their experience with the treatment of cryptococcal meningitis, that there is a correlation between the spinal fluid protein level and the passage of amphotericin B into the cerebrospinal fluid. This might explain the apparently good initial response to intravenous treatment of the neurological disease in our patient, followed later by neurological relapse. An effective level of amphotericin B in the spinal fluid may have been obtained only during the first part of the second and third courses of intravenous treatment.

Intrathecal amphotericin B has been used mainly in the treatment of cryptococcal meningitis, and some good results have been obtained

(2, 7-9). In most instances, concurrent intravenous treatment has been given, and the part played by the intrathecal treatment is difficult to assess. An exception is a case (12) where intravenous treatment was interrupted by recurrent azotemia, and amphotericin B was continued by the intrathecal route alone for a period of two and one-half months, with good results.

Transient paresthesias have been noted following intrathecal injection, and Seabury and Dascomb (2) noted transient paresis in the left lower extremity of one patient, which subsided within 72 hours. The paraplegia which occurred following the sixth intrathecal instillation in our patient was more serious and prolonged, and led us to discontinue intrathecal treatment. Wilson, Rupp, and Wilson (13) warned in 1949 that "the introduction of each new therapeutic agent into the intrathecal space has been inevitably followed by reports of serious damage to the nervous system." Assessment of the dangers and of the advantages of using the intrathecal route in treatment with amphotericin B must await the accumulation of further experience. To date our patient has shown no signs of further relapse, and it may be that the three-week course of intrathecal treatment which he received helped him. Continued follow-up for some time will of course be necessary before a definite conclusion can be reached about the results of treatment.

SUMMARY

A case of disseminated blastomycosis is described in which two neurological relapses occurred after treatment with intravenous amphotericin B. After the second relapse, the drug was given intrathecally as well as intravenously, but intrathecal treatment was interrupted by the development of paraplegia.

ADDENDUM

The patient has continued under observation as an outpatient since this report was prepared. He was last seen on March 13, 1961, at which time he felt well generally and had no evidence of relapse of blastomycosis. Neurological findings were unchanged from those found on examination March 7, 1960. The most recent examination of cerebrospinal fluid, done on

December 12, 1960, showed a sugar content of 81 mg/100 ml, protein 56 mg/100 ml, and 5 cells/mm³.

ACKNOWLEDGMENT

We wish to thank Dr. M. L. Furcolow for his advice and laboratory assistance, and for his help in preparing this paper.

SUMMARIO IN INTERLINGUA

Blastomycosis disseminate pote afficer le pulmones, le pelle, le vias genitourinari, tissu molle, osso, e le systema nervose central. Amphotericina B, administrate per via intravenose, pare esser le tractamento le plus successose pro iste condition. Le presente reporto concerne un patiente con blastomycosis disseminate qui apparentemente respondeva ben a intravenose amphotericina B sed qui subsequentemente suffreva duo recidivas neurologic. Post le secunde recidiva, amphotericina B esseva administrate etiam intrathecalmente, sed iste via de administration esseva abandonate post le desenvolvamento de paraplegia.

Un masculo de racia blanc de 67 annos de etate esseva hospitalisate un mense post le desenvolvamento de febre de origine incognite, sequite per signos e symptommas prostatic. Un roentgenogramma thoracic monstrava un configuration miliari a transverso ambe campos pulmonar. Un mense post le admission al hospital un eczema papular se manifestava, e le diagnose de blastomycosis disseminate esseva formulate, justificate per un positive test de fixation de complemento e le constatacion de typic organismos in le lesiones cutanee. Nulle signos o symptommas de morbo neurologic esseva presente a ille tempore.

Amphotericina B esseva administrate per via intravenose durante un periodo de octo septimanas, amontante a un total de 1,594 g. Le restablimento del patiente pareva progredere ben, con disparition del eczema cutanee e del anormalitates in le roentgenogramma thoracic. Dece-un septimanas plus tarde le patiente esseva re-hospitalisate con le gravamines de mal de capite, febre, debilitate general, e recente manifestaciones de confusion. Brevemente post su admission ille disveloppava paralyse sinistro-facial e hemiplegia dextere. Le liquido cerebrospinal monstrava augmento de proteina, reduction de suero, e 172 lymphocytos per millimetro cubic. Esseva notate nulle indication de un recurrentia de blastomycosis in le pulmones o le pelle. Le administration intravenose de amphotericina B

esseva re-instituete. Le responsa clinic esseva bon, e le constataciones in le liquido spinal se meliorava. A iste occasion le tractamento intravenose esseva continuate durante 12 septimanas, amontante a un dose total de 2,473 g. Al fin de iste curso, le patiente esseva de novo libere de symptommas. Ille continuava trovar se ben durante un periodo additional de octo septimanas, sed alora ille redisveloppava mal de capite e debilitate e redeveniva confuse. Ille esseva readmittite al hospital, e su liquido spinal monstrava de novo lymphocytosis, augmento de proteina, e reduction de suero. Le tractamento con amphotericina B esseva instituete ancora un vice, e le patiente respondeva ben a iste tractamento intravenose. A causa del repetite recidivas neurologic, il esseva decidite administrar le droga non solmente per via intravenose sed etiam per via intrathecal. Instillationes esseva facite per puncturas lumbar duo vices per septimana. Isto resultava in nulle adverse effecto usque post le sexte injection intrathecal, quando ille disveloppava debilitate e torpor in ambe gambas e anormalitates del innervation vesical. Le paraplegia se meliorava in le curso del sequente quatro septimanas e—in le curso del tempore—dispareva sin signos residue. Observaciones ulterior ha revelate nulle signo de recidiva de blastomycosis usque a septe menses e medie post le completion del tertie curso de tractamento.

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Acute Cerebellar Syndrome Secondary to Infectious Mononucleosis in a Fifty-two Year Old Man

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THE CASE OF INFECTIOUS MONONUCLEOSIS PRESENTED is of interest in that it occurred in a patient in the older age group, and that the central nervous system involvement manifested as an acute cerebellar syndrome.

CASE REPORT

A 52-year-old white male office worker was admitted to The University of Wisconsin Hospitals on December 12, 1958, complaining of incoordination, weakness, and slurring of speech. Three weeks previously he had developed a sore throat, fever, malaise, headache, and cough. He was treated with penicillin and the symptoms subsided in several days. Two weeks before admission he noted unsteadiness in walking and difficulty in punching the time clock at work. A week before admission a syncopal attack lasting for several seconds and unassociated with aura or convulsive activity resulted in referral to the local hospital. While hospitalized his ataxia and subjective vertigo increased to such an extent that he had to remain in bed. Because of the progressive course of his illness, he was referred to our hospital.

Past medical history indicated that five years previously he had had bilateral nephrolithotomies for renal calculi.

Family history and review of systems were entirely negative. There was no known exposure to toxic agents or infectious diseases, no history of

excessive alcoholic intake, and no history of allergy to penicillin.

On admission the patient's temperature was 98.6° F; blood pressure, 120/80 mm Hg; respiration, 20; pulse, 60. The patient was alert and cooperative, but his speech was slurred and at times explosive. There was slight pharyngeal injection, but no lymphadenopathy, hepatomegaly, or splenomegaly was noted. Neurological examination revealed no papilledema. Pupils reacted to light and accommodation. Peripheral fields and extraocular movements were normal. No nystagmus was noted. The remainder of the cranial nerves were within normal limits. Although strength was normal, there was moderate hypotonia in all extremities. Marked dysmetria was noted on finger-to-nose and heel-to-shin tests bilaterally. There were slightly decreased deep tendon reflexes without Babinski's or confirmatory signs. On attempting to walk he displayed a markedly widened base and severe ataxia. There was a tendency to marche à petits pas. Sensory examination was normal. There was no nuchal rigidity or muscle tenderness.

Laboratory data revealed a white count of 8,000/mm³, with 49% lymphocytes, of which approximately 6% were atypical. These showed staining and morphological characteristics similar to those reported in infectious mononucleosis. The remainder of the blood count showed 43% neutrophils, 3% basophils, 3% monocytes, and 2% eosinophils. Hemoglobin was 15 g/100 ml. An absorbed heterophil antibody of 1:512 was noted. Bromsulfalein was 8%; thymol turbidity, 8.7 units; alkaline phosphatase, 18.7 Bodansky units; total protein, 6.7 g/100 ml; albumin, 3.9 g/100 ml; globulin, 2.8 g/100 ml. The cerebrospinal fluid was under normal pressure, and showed 1 polymorphonuclear cell per high power field, a protein of 20 mg/100 ml, normal sugar and chloride concentrations, and normal gold sol curve. Chest and skull X rays were nor-

Received for publication March 21, 1960.

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mal. Cultures of the spinal fluid for routine organisms, fungi, and acid-fast bacilli were negative. Cultures of the stool for poliomyelitis, enterocytopathogenic human orphan virus, and Cox-sackie virus were negative. Blood studies for Asian influenza and other common encephalitides were within normal limits in both acute and convalescent sera.

For the first few weeks following hospitalization the patient's condition remained essentially unchanged. By the end of December his speech had improved and he had lost his subjective feeling of vertigo. There was a slight decrease in dysmetria and ataxia on walking. During the first week of January there was marked improvement in his condition. He could walk without support, no dysmetria was present on finger-to-nose or heel-to-shin tests, and speech had improved considerably. At this time the absorbed heterophil antibody titer was 1:128, the alkaline phosphatase had fallen to 10.7 Bodansky units, and the thymol turbidity was 4.6 units. The peripheral smear showed normal count and morphology of the white blood cells. The patient was discharged on January 8, 1959, and follow-up examination in February and March showed no abnormal neurological symptoms or signs. At these examinations the absorbed heterophil antibody titer was 1:32, and the white blood count and liver function studies were within normal limits. The patient had returned to work and was experiencing no untoward effects from his illness.

DISCUSSION

Although infectious mononucleosis is primarily a disease of the second and third decades of life, cases have been reported in patients as young as seven months (1) and as old as 77 years (2). Only five cases have been reported in patients over the age of 60 (2).

Less than 1% of cases of infectious mononucleosis have neurological complications (3). These have been classified by Bernstein and Wolff (3) into serous meningitis, meningitis, meningo-encephalitis, acute polyneuritis, and peripheral neuropathy associated with encephalitis. The acute polyneuritis has been reported most frequently. An acute cerebellar syndrome as a manifestation of the encephalitic process is quite rare. Only two cases have been reported in the literature, both patients in their late teens, with histories and clinical findings similar to those in our patient (4, 5). Both recovered without sequelae.

The onset of cerebellar signs and symptoms in the older age group is usually indicative of a degenerative, demyelinating, vascular, or neo-

plastic disease. With these, the prognosis is quite poor. However, one should keep in mind the acute cerebellar syndromes occurring with or following primary or secondary infections of the nervous system, usually viral. Although this has been established as a definite clinical entity in children (6, 7), it has not been well documented in the adult. The prognosis in these cases is usually good.

A case of an acute cerebellar syndrome secondary to infectious mononucleosis in an adult is presented. Only two cases have been reported previously in the literature. Mention is made of the similarity of this case and the acute cerebellar syndrome usually associated with viral diseases in children.

SUMMARY IN INTERLINGUA

Duo septimanas post un maladia febril associate con mal de gurgite, cephalalgia, e tusse, un masculo de racia blanc de 52 annos de etate disveloppava signos e symptomas de progressive discompensation cerebellar. Le examine physic general esseva normal. Le examine neurologic monstrava hypotonia, reducite reflexos, un ambulatura ataxic, e marcate dysmetria in tests del extremitates. Le lymphocytos in frottis peripheric monstrava le alterationes morphologic characteristic de mononucleosis infectiose. Le titro de absorbite anticorpore heterophile esseva 1:512. Le examine del liquido spinal esseva normal. Le curso subsequente del patiente esseva marcate per melioration gradual. Tres menses post le declaration del morbo, ille monstrava nulle evidentia de residuos.

Minus que 1% del casos de mononucleosis infectiose ha complicationes neurologic. Istos ha essite classificate in meningitis serose, meningitis, meningo-encephalitis, polyneuritis acute, e neuropathia peripheric associate con encephalitis. Un acute syndrome cerebellar como manifestation del processo encephalitic es multo rar. Solmente duo altere casos se trova reportate in le litteratura. Mononucleosis infectiose in iste gruppo de etate es rar. Solmente cinque casos es reportate in patientes de etates de plus que 60 annos. Le apparition de signos e symptomas cerebellar in iste gruppo de etate indica usualmente un irreversibile processo sever del typo causate per morbo vascular, degenerative, metabolic, o neoplastic.

Tamen, on non debe oblidar le acute syndromes cerebellar secundari a infectiones viru-

sal in que le prognose es usualmente bon. Ben que iste syndrome es ben documentate in juveniles, su occurrentia in adultos non es ben cognoscite.

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Post-Traumatic Hypopituitarism

Anterior Pituitary Insufficiency Following Skull Fracture

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ONE OF THE RAREST CAUSES of anterior hypopituitarism is a lesion of the pituitary gland following a skull injury. Fourteen cases have been reported in the literature to date.

The rarity of these cases and the importance of making an early diagnosis so that proper treatment may be instituted and chronic morbidity, as well as medicolegal aspects, avoided prompt us to report an additional case.

CASE REPORT

A 68-year-old carpenter was admitted because of fever, increasing weakness, anorexia, and diarrhea. Physical examination revealed an acutely ill man who looked younger than his years. He was very pale. Blood pressure was 80/60 mm Hg; pulse, 96/min; temperature, 37.4°C. The skin was soft and there was a complete lack of axillary hair; only single hairs grew in the pubic area (Figures 1, 2). The testes were atrophic and lentil-sized. The prostate was small. A scar was noticed in the right frontotemporal region. There was enophthalmos. This brief clinical examination seriously suggested

the possibility of anterior hypopituitarism. The condition was diagnosed as an Addisonian crisis and treatment was promptly instituted. A few days later, when his general condition improved, the following details were obtained.

Until five years previously the patient had been in perfect health and working hard as a carpenter. His libido and potency in spite of his age were very good. Suddenly he had been struck down by a car, and suffered a fracture of the skull. X-ray examination showed a right frontotemporal linear fracture with some probable damage to the clinoid processes (Figure 3). The cerebrospinal fluid was slightly hemorrhagic, but the patient did not lose consciousness. Neurological and ophthalmological examinations were negative. He was discharged 18 days after admission.

Two or three weeks later he noticed that his hair was falling out, particularly that of the axillae and the pubic area, and less so from the scalp and eyebrows. There was a complete loss of libido and potency. He also became aware of a marked decrease in the size of his testicles. Since the accident the patient had also noticed marked lack of energy, fatigue, and weakness. As he was used to an active life this proved distressing. He noted great sensitivity to cold, and his family perceived personality changes of mental dullness and a persistent somnolent mood, interchanging with aggressive, paranoid thoughts. For years he had visited physicians and had been diagnosed as a post-traumatic case of neurosis.

A few days before admission he had suffered an intercurrent infection, which precipitated the adrenal crisis for which he was admitted.

Received for publication April 18, 1960.

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FIGURE 1. Note complete absence of axillary and chest hair, small, nonpigmented mamillae, deformation of right orbital region.

LABORATORY EXAMINATION

Blood sedimentation rate, 50 mm in the first hour; normocytic, normochromic anemia. Hemoglobin, 10.6 g/100 ml; red blood cells, 3.3 million/mm³; hematocrit, 29%. Plasma iron, 59 µg/100 ml; blood sugar (Somogyi), 68 mg/100 ml; plasma vitamin B₁₂, 150 µg/100 ml; plasma sodium, 130 mEq/liter; plasma potassium, 4.3 mEq/liter; CO₂-combining power, 55 vol%; blood urea, normal. A glucose tolerance test showed a flat curve.

Adrenal Function Studies:

1. Urinary 17-ketosteroids (Callow's modification of Zimmerman reaction), 0.6 to 0.9 mg/24 hr (normal range at 68 years: 2 to 10 mg/24 hr).
2. Urinary 17-hydroxysteroids (Norymberski method), 3 to 5.8 mg/24 hr (normal range at 68 years, 5 to 17 mg/24 hr).
3. Water diuresis (per cent of dose excreted in three hours). Normal: 70%.
 - a. Without administration of cortisone, 35%.
 - b. With administration of cortisone, 90%.
4. Thorn test: Initial count, 850 eosinophils/mm³; four hours after administration of 25 units

ACTH, 325 eosinophils/mm³; after eight hours, 50 eosinophils/mm³.

5. Intravenous infusion test, 25 units ACTH:

- a. 17-ketosteroids before ACTH infusion, 0.8, 0.6, and 0.9 mg/24 hr (three successive days).
- b. 17-ketosteroids after ACTH infusion, 1.2 mg/24 hr.
- c. 17-hydroxysteroids before ACTH infusion, 5.8, 3.0, and 3.4 mg/24 hr.
- d. 17-hydroxysteroids after ACTH infusion, 7.2 mg/24 hr.

Thyroid Function Studies:

1. Basal metabolic rate determination was not performed (see text).
2. I¹³¹ uptake at 48 hr, 20%. Urinary excretion in 48 hr, 80%.
3. Protein-bound iodine, 3.1 µg/100 ml.
4. Plasma cholesterol, 222 mg/100 ml.

Urinary excretion of follicle-stimulating hormone, less than 30 rat units/24 hr.

The electrocardiogram showed normal voltage, small P waves, and slight inversion of the T waves. The electroencephalogram showed a generally disturbed pattern with a slow wave frequency. The



FIGURE 2. Note almost complete absence of hair in pubic area.



FIGURE 3. X ray of skull taken after accident. A right frontotemporal linear fracture is seen.

eye examination showed no disturbances in the fundi or perimetry.

X ray of Skull: A healed fracture of the right frontotemporal region was noted, as well as a wavy course of the sella turcica, sclerotic changes in the floor, and intrasellar calcifications (Figure 4).

COMMENTS ON CASE REPORT

The clinical picture and laboratory examination showing involvement of the thyroid, gonads, and adrenals, together with low urinary excretion of follicle-stimulating hormone, the history of cranial trauma, and X-ray evidence of injury to the sella satisfied all the criteria

required for the diagnosis of post-traumatic anterior hypopituitarism.

A similar case has been described without roentgenological support (1).

There was no diabetes insipidus or obesity, no disturbance in the temperature regulation, and no pyramidal or sensory changes. The patient's inability to recover from the serious accident was perhaps the first sign of an impaired integration of his endocrine system. Later, a decrease in sexual function and a falling out of the hair occurred.

For five years the case was not diagnosed and



FIGURE 4. X ray of skull taken at present admission. Note wavy course of the sella turcica, sclerotic changes in the floor, and intrasellar calcifications.

consequently the disease was not rationally treated. This delay in diagnosis, sometimes lasting many years, is still a well-known phenomenon in hypopituitarism, especially in men. This, no doubt, is due to the great variations presented by the clinical picture, because of either failure of various pituitary functions at different rates or a combination of complaints not easily classified. A certain resistance on the part of physicians to get information on libido and potency and misinterpretation of these disturbances probably also play a role.

According to Hubble (2) sexual functions are almost always the first to be involved in the course of anterior hypopituitarism. According to others the first signs are those of anemia and weakness (3).

The endocrine work-up of our patient failed to show a significant rise of urinary excretion of 17-ketosteroids and 17-hydroxysteroids after the eight-hour ACTH intravenous infusion test. This, perhaps the most critical test in differentiating primary from secondary adrenal failure, did not show the expected rise of 100 to 300% excretion of 17-hydroxycorticosteroids. Most probably the long-standing lack of endogenous ACTH caused some atrophy of the adrenals, which were not stimulated immediately. We should have continued the ACTH infusions for another day or two.

There were no episodes of hypopituitary coma in our patient. However, twice he passed into addisonian crisis, the first time while suffering an intercurrent infection, and the second time when a determination of basal metabolic rate was attempted. The patient got so frightened by the sight of the apparatus that this "stress" precipitated crisis, although the examination had not yet started. A standard insulin tolerance test (4) was also not performed because of the well-known dangers of this examination (5, 6). Patients with hypopituitarism are very sensitive to insulin administration (7). There have been reported cases of hypopituitary coma (8) or even death after administration of small amounts of this hormone (9). Following treatment with Meticorten, thyroid extract, and methyltestosterone his condition improved remarkably. The fatigue and weakness disappeared and the mental changes showed marked improvement. The electroencephalographic tracing remained unchanged. Two months after

the beginning of therapy his libido and potency improved. One year later, in a follow-up visit, his general condition was good. The sensitivity to cold had lessened. The patient was working and active.

DISCUSSION

Cushing (10) described a case of death due to acute pituitary cachexia three days after accidental division of the pituitary stalk during a cranial operation. Others have also reported cases of death a short time after operation or trauma in the region of the pituitary gland, or after the appearance of metastases there (11, 12). In these cases severe necrosis of the anterior pituitary was found at autopsy, caused by a disturbance in the blood supply to this region.

Daniel, Prichard, and Treip (12) described extensive infarctions of the anterior pituitary lobe due to rupture of the pituitary stalk in five fatal cases after head injury. According to them the possibility of small, functionally insignificant infarcts of the anterior pituitary exists in cases of hypertension, increased intracranial pressure, or head injury. These small infarcts are not due to rupture of the pituitary stalk, but are presumably due to a very localized cessation of the circulation in only part of the stalk. In their opinion "the regeneration of pituitary portal vessels and of anterior lobe cells is possible. It may explain why a relatively large proportion of patients shows signs of temporary mild hypopituitarism after head injury, although severe post-traumatic Simmond's disease is rare."

It appears that cases of chronic post-traumatic anterior hypopituitarism belong to the group in which the severity of the trauma and damage to the gland and pituitary stalk are not sufficient to cause death. On the other hand it is sufficiently severe so that regeneration of the blood vessels and anterior lobe cells is made impossible.

According to Robertson and Kirkpatrick (1) the syndrome described by Frank (13) in 1912 fits the picture of anterior hypopituitarism caused by a bullet wound in the region of the pituitary gland, but his description was not clear. Escamilla and Lissner (14) found, out of 595 cases of Simmond's disease, only one case caused by trauma, and added four other similar cases from the literature. In their words, the

first case of post-traumatic Simmond's disease was described by Cyran in 1918 (15). Until 1953 only 11 cases had been published (6), not including the case of Frank. It is possible that one of the cases of Koepf and Vieillard (16) also belongs in this group. In one of the patients described by Porter and Miller (17) anterior pituitary insufficiency as well as diabetes insipidus developed after a closed head injury. Epilepsy also appeared in two patients with post-traumatic hypopituitarism (18). Lafon, Passouvant, Labange, and Bonnet (19) in 1955 reported a case of myotonic syndrome in post-traumatic pituitary myxedema. This last case raised the total number of cases of post-traumatic anterior hypopituitarism known to us to 14. It is not clear if the decrease in libido and potency after head injury, described by Stier (20), was caused by a lesion in the anterior pituitary.

In our opinion, in every case of anterior hypopituitarism of undetermined etiology, (13, 16, 21), attention must be paid to any history of head injury. On the other hand, one should pay attention to the possibility of anterior hypopituitarism in those patients with a change in personality whose illness has been diagnosed until now as post-traumatic neurosis.

These cases also present some medicolegal aspects. No doubt the right of the patient to claim damages for his hypopituitary state would be upheld. To the best of our knowledge no previous claim based on this disease has yet been made.

SUMMARY

A case of post-traumatic anterior hypopituitarism is described, bringing to 15 those reported in the literature. The diagnosis was not made until five years after the start of the disease, when the patient was hospitalized because of an adrenal crisis precipitated by an intercurrent infection.

Cases of chronic post-traumatic anterior hypopituitarism are very rare and the diagnosis is usually made late in the course of the disease. This emphasizes the variability of the clinical picture and the insufficient attention which has been paid to this entity.

Combined treatment with Meticorten, thyroid extract, and methyltestosterone rapidly

improves the condition of the patient and seems to us the most feasible method.

The possible medicolegal aspects of these cases are also mentioned.

ACKNOWLEDGMENT

We are indebted to Dr. A. Gefel, Chairman of the Department, for helpful critical comment.

SUMMARY IN INTERLINGUA

Un del causas le plus rar de chronic insufficientia antero-pituitari es un lesion del glandula pituitari in consequentia de un injuria cranial. Usque nunc solmente 14 casos se trova reportate in le litteratura. Casos de morte per hypopituitarismo acute post trauma cranial non es exceptional in ille serie. In tal casos, sever necrosis del pituitario anterior esseva constatate e explicate como effecto de un disturbance del provision de sanguine. Del altere latere, regeneration de vasos pituitario-portal e del cellulas del lobo anterior es possibile, lo que explica possiblementemente proque un relativemente alte proportion del patientes manifesta signos de leve e transiente hypopituitarismo post trauma al capite, ben que sever morbo de Simmond post trauma es rar.

Nostre patiente, un masculo de 68 annos de etate, esseva acutemente malade quando ille esseva hospitalisate a causa de infection intercurrente. Le pelle esseva molle, pallide, e sin capillos. Le testes esseva atrophic e le prostata micre. Esseva notate un cicatrice in le region fronto-temporal al latere dextere, con enophthalmia. Le diagnose esseva crise addisonian, e le correspondente tractamento esseva institute immediateamente.

Usque cinque annos prevemente, le patiente se habeva portate ben. Ille esseva atterrate violentemente per un automobile e suffreva un fractura fronto-temporal al latere dextere. Le examines neurologic e ophthalmologic esseva negative. Duo o tres septimanas post le accidente, su capillos comenciava cader, su libidine e su potentia sexual dispareva, e le dimensiones de su testes regrededa progressivamente. Ille suffreva de un marcate manco de energia, de debilitate, sensibilitate pro frigido, e alterationes mental. Durante un numero de annos, le caso de iste patiente esseva diagnosticate como neurose post-traumatic.

Al tempore del hic reportate hospitalisation, le examine laboratorial revelava normocytic anemia normochromic, hypofunction del glandulas thyroide, adrenal, e gonadic, e un basse

excretion urinari de hormon folliculo-stimulante. Le examine ophthalmologic esseva negative. Un resanate fractura del region fronto-temporal al dextera e un curso undulante del sella turcic con alterationes sclerotic in le fundo e calcification intrasellar esseva notate in le examine roentgenographic. Iste tableau clinic e laboratorial, insimul con le anamnese de trauma cranial e evidentia roentgenographic de trauma al sella turcic, satisfaceva omne le criterios de un diagnose de insufficientia post-traumatic del pituitario anterior. Post tractamento con Meticorten, extracto de thyroide, e methylestosterona, le condition general del patiente se meliorava remarcabilemente.

In iste caso, le condition habeva remanite non-diagnosticate durante un intervallo de cinque annos. Tal retardos del diagnose es un ben-cognoscite phenomeno in casos de hypopituitarismo in masculos, probabilemente a causa del grande variationes que characterisa le tableau clinic. In nostre opinion, in omne caso de insufficientia del pituitario anterior de etiologia indeterminate, attention debe esser prestate al possibilitate de un anamnese de trauma al capite. In omne caso de neurose post-traumatic il existe al minus le possibilitate de insufficientia del pituitario anterior. Aspectos medico-legal de tal casos es sublineate.

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Hereditary Spherocytosis with Fatal Complications

Necessity of Elective Splenectomy Early in the Disease

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HEREDITARY SPHEROCYTOSIS IS A DISEASE characterized by the inherited abnormality of spherocytic red cells, associated with varying degrees of hemolytic anemia and jaundice. Splenectomy in this disorder is usually effective in causing a cessation of the excessive red cell destruction and relieving the anemia and jaundice. If it is performed early in the course of the disease subsequent disability, including biliary tract complications, is eliminated. It is generally agreed that splenectomy is necessary when anemia, jaundice, and hemolytic or aplastic crises are troublesome (1). However, it has not been emphasized that complications of this disease may shorten life expectancy, and that splenectomy should be performed soon after the diagnosis has been established. The following case study is considered to be illustrative in this regard.

CASE REPORT

A 58-year-old white male was admitted to the Bristol Memorial Hospital for the first time on January 14, 1955, because of jaundice of several days' duration. There was no family history of anemia or jaundice at that time. He had had recurrent episodes of jaundice since childhood. The last severe attack had occurred seven years before, and had subsided spontaneously over a period of several days. He was seen at that time by another physician, and the diagnosis of hereditary spherocytosis was established. Splenectomy was advised but was rejected by the patient as the jaundice was diminishing at the time. He felt well generally, denying such symptoms of anemia as dyspnea, weakness, or easy fatigability. Onions were said to cause gas and epigastric distress, but there were no other gastrointestinal complaints. Jaundice had developed insidiously one week before admission and had progressively deepened. Five days before, he had had severe right upper quadrant and epigastric pain that lasted about four hours. After this the urine became very dark and the stools clay colored.

Received for publication April 4, 1960.

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The temperature was 98.6 F; pulse, 80; respirations, 16; and blood pressure 130/80 mm Hg. The skin was intensely icteric and the sclerae were deep orange in color. He was well developed and well nourished and did not appear to be ill except for jaundice. There were no spider telangiectases, liver palms, or other stigmata of liver disease. The abdomen was moderately obese and an indefinite mass was palpable in the left upper quadrant.

The red cell count was 3.9 million per mm³, hemoglobin, 11.5 g per 100 ml, and the hematocrit, 37%. The white cell count was 5,600/mm³ with a slight shift to the left. Many spherocytes were seen in smears of the peripheral blood. The sedimentation rate (Wintrobe) was 9 mm in one hour. The Kahn serological test was negative. Urinalysis contained no albumin or sugar; sediment was normal but strongly positive for bilirubin. The total serum bilirubin was 8.5 mg per 100 ml, with 1.6 mg per 100 ml direct and 6.9 mg per 100 ml indirect. Osmotic fragility of the red cells began at 52% (control .48%), and was complete at .32% (control .36%). The cephalin flocculation was negative in 48 hours, and the thymol turbidity was 1.2 Maclagan units. Blood sugar at admission was 93 mg per 100 ml fasting, and the blood urea nitrogen was 16 mg per 100 ml. The one-stage prothrombin time was 100% (control and patient, 13.5 seconds). The Coombs' test was negative both direct and indirect, and screening tests for warm, cold, and acid hemolysins and agglutinins were normal.

The diagnoses of hereditary spherocytosis and obstructive jaundice due to common duct biliary stones were made. Three days after admission he was advised to have a splenectomy and common duct exploration, but he refused. However, the jaundice continued to deepen and he consented to surgery on the sixth hospital day. A large spleen was removed with minimal difficulty. The gall bladder was packed with small stones. The pancreas was felt to be indurated, but no fat necrosis or other evidence of acute inflammation was seen at that time. The common bile duct contained many small pigment-type stones; it was blocked with a thick, tenacious, tar-like bile precipitate that was difficult to remove. Obstruction of the duct was complete, necessitating a transduodenal approach to the ampulla of Vater. Sphincterotomy was necessary to cleanse the duct and a long limb T tube was inserted into the common duct and the duodenum to maintain drainage. The gall bladder was then removed. Tachycardia developed and persisted, ranging between 130 and 170. The blood

pressure was maintained well throughout the operation, varying between 140 to 120 systolic and 80 to 70 diastolic. The patient received three pints of blood during the surgical period of three hours and 35 minutes.

During the first postoperative day tachycardia persisted between 120 and 130 and fever between 101 and 103 F rectally. He was given digitalis, but for the remainder of the hospital stay the pulse was elevated between 110 and 130. Blood pressure varied between 110/70 and 130/90 mm Hg. Penicillin and streptomycin, started on the second day, were continued; during the first five days he received tetracycline. Nasogastric suction was started routinely after the operation, was discontinued on the third day, and was reinstituted within 24 hours because of severe distention and ileus. He never complained of abdominal pain but remained tender to palpation over the entire abdomen. Fever varied between 100 and 102 F rectally for the entire postoperative period. By the fifth day the blood urea was 138 mg per 100 ml, despite a daily urinary output greater than 1,500 ml from the second day.

He received adequate quantities of intravenous saline, glucose, and potassium. On the fifth day cortisone, 50 mg intramuscularly every 12 hours, was begun as a supportive measure. His general condition continued to deteriorate, and from the eighth day on he was kept in an oxygen tent. Despite the continuation of supportive therapy he died on the twelfth postoperative day in peripheral vascular collapse.

At autopsy massive hemorrhagic pancreatic necrosis was found with areas of fat necrosis. A common channel was formed by the junction of the common bile duct and the main pancreatic duct. There were no evident thromboses or other injuries to the arterial blood supply to the pancreas. Microscopically a chronic interstitial pancreatitis was seen, suggestive of previous occlusions of the ampulla of Vater. Some of the pancreatic ducts were seen to be dilated and to contain yellow bile pigment. Cholemic nephrosis was also described. The spleen weighed 450 g and showed hemosiderosis, fibrosis, and hyperplasia of the endothelial cells lining the sinusoids. The liver revealed hemosiderosis, hepatocellular damage, and multiple bile thrombi in the canaliculi. A 3.5 cm accessory spleen was imbedded in the tail of the pancreas. Acute hemorrhagic pancreatic necrosis was thought to be the primary cause of death.

After his death, his five children were studied, and one son, age 33 years, was found to have hereditary spherocytosis. He underwent splenectomy elsewhere uneventfully. No biliary stones were found. He had mild anemia and jaundice that subsequently cleared. Easy fatigability and weakness that had always troubled him disappeared after surgery.

DISCUSSION

The most unusual feature of this case was the complete obstruction of the common bile

duct due to the tar-like precipitated bile and multiple small biliary calculi of the pigment type. The fatal pancreatic necrosis was thought to be secondary to this obstruction of the common duct in keeping with the common channel theory (2). It is possible that the long limb T tube may have produced obstruction and pancreatitis as reported by Thompson, Howard, and Vowles (3). However, others have not found the incidence of pancreatitis as a complication in upper abdominal surgery to be increased as a result of the use of a long limb T tube (4). As reviewed in the latter article, pancreatitis is a serious complication of upper abdominal surgery, particularly biliary and gastroduodenal. Also the transduodenal approach as used in this case with sphincterotomy is associated with a higher incidence of pancreatitis as a complication. This is even more likely if subacute pancreatitis is already present (4). The finding of evidence of previous pancreatitis at surgery and at autopsy adds to the belief that the complete obstruction of the common duct was the main etiological factor in this case. The surgical factors mentioned may also have been of primary or additive importance.

It was thought by all concerned that all the operative procedures carried out were necessary. It would have been unwise to explore and clean the common duct and remove the gall bladder without performing a splenectomy. Excessive hemolysis would have continued and probably new pigment stones and precipitated bile would have caused further difficulty, with common duct blockage and obstructive jaundice and pancreatitis. Possibly, the patient might have fared better if surgery had not been delayed the additional three days after it was first proposed. It is indeed probable that if splenectomy had been performed in this case when the diagnosis was first established seven years earlier he would not have died from these complications. This would have been true particularly in an asymptomatic interval when the patient was not having a hemolytic crisis with jaundice and anemia. It is well established that the excessive hemolysis associated with this disease leads to the formation of biliary calculi of the pigment (bilirubin) type, and the incidence of gallstones has been reported to be as high as 80% (1).

This case shows that the complications of

excessive hemolysis, with formation of biliary stones, common duct obstruction, and fatal hemorrhagic necrosis of the pancreas, may develop in a patient with hereditary spherocytosis. Therefore, it is proposed that all patients with this disease have splenectomy as soon as is feasible after diagnosis is established, to prevent these complications. In view of the reported increased risk of serious infections after splenectomy in very young children, operation would best be deferred until later in childhood unless the patient were ill with anemia (5).

SUMMARY

A case of hereditary spherocytosis with death due to biliary tract obstruction and acute hemorrhagic pancreatic necrosis is presented. As the diagnosis had been established seven years previously, it is probable that earlier splenectomy would have prevented these complications and that this patient would have had a normal life expectancy. Splenectomy should be performed in all patients early in the course of this disease, as soon as is practicable after the diagnosis is established.

SUMMARIO IN INTERLINGUA

Splenectomy es generalmente considerate como necessari in casos de spherocytosis hereditari si jalnessa e anemia es presente. Tamen, il non se trova sublineate in le litteratura que le splenectomy in tal casos deberea esser effectuate precocemente pro prevenir le complicationes causate per obstruction del vias biliari, per pancreatitis, o per ambe iste conditiones. Es presentate un caso in que le diagnose de spherocytosis hereditari esseva establite e in que splenectomy esseva recommendate. A ille tem-

pore le patiente refusava le operation, proque su symptomatos esseva leve, e le jalnessa subsideva spontaneamente, como illo habeva subsidite frequentemente in le curso de su vita. Septe annos plus tarde le operation esseva executate a causa de completamente obstructive jalnessa causate per multiple calculos biliari e inspissate catranose bile. Splenectomy, cholecystectomy, e exploration del ducto biliari con mundation esseva necessari. Post le operation, acute pancreatitis hemorrhagic se disveloppava, e le patiente moriva. Le causas possibile del pancreatitis post-operatori es discutate. Viste que le necropsia produceva evidentie de un previe pancreatitis, il esseva concludite que blocage del ducto commun esseva le factor principal. Es presentate le these que omne patientes con iste morbo deberea esser subjecite a splenectomy si tosto que le diagnose es establite. Le excessive hemolyse erythrocytic cessarea allora e etiam le formation de multiple calculos biliari del typo a pigmento. Complicationes, como le obstruction del ductos biliari e le pancreatitis describite in le presente caso, esserea prevenite.

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SPECIAL ARTICLE

Presidential Address

CHESTER S. KEEFER, M.D., F.A.C.P., *Boston, Massachusetts*

TONIGHT YOU ARE BEING ADMITTED TO Fellowship in the American College of Physicians, so I hasten to extend to you a very sincere welcome.

We, who have been Fellows for some time, have learned to appreciate the intellectual value of such a Fellowship. We know that your experience will duplicate ours. We are proud to have you as Fellows because we recognize that the College will grow only through the medium of new members who have met the high standards for admission and election. We know that you will bring to the College new ideas, new inspirations, and new strengths.

It is our sincere desire then to welcome you, secure in the knowledge that, just as the College has something for you, you in turn have much to contribute to us.

The American College always has an eye toward tomorrow. We view these annual sessions as occasions to look forward more than back, and we center our attention on the broad medical problems of today and tomorrow.

We are not unmindful of the fact that the social evolution of our society that has been going on at a fast moving pace during the past 50 years has had a profound effect upon health and happiness. Health is here defined as a state of human excellence, and happiness as a state in pursuit of accomplishment.

This week we have been exploring some of the advances in science and technology as applied to improving health and happi-

ness, and we have been studying many questions and problems and seeking the answers and the solutions. We live in an age of progress, that is, an age of promise.

THE CHANGING MEDICAL SCENE

The medical world into which we were born is gone. The American medicine of the past has transformed itself. We have little or no idea of the medical world into which we may grow tomorrow. Big changes are taking place. But it is not the change itself that I see as the dominant factor today, *it is the rate of change.*

The old order of medical practice is giving way to the new. Instead of physician and patient, we hear about the producer and the consumer. Instead of the doctor providing and rendering professional service, we hear about the merchandising of medical care and its commodity value. The mental picture that many Americans carry with them about medicine and medical care is lamentably irrelevant to the real situation of today, and the changes that have taken place on the American scene are not fully grasped.

The concepts of the medical profession tend to date sharply, particularly when we get into arguments or public debates.

When the spokesmen of organized medicine decide to say a few words on behalf of "freedom of choice" or "individual doctor-patient relationship" and against "group practice" or "socialized medicine," one is suddenly aware that the image of individual doctor-patient relationship in their minds looks more like the horse and buggy doctor, or the old portraits of the doctor by Luke Fildes or Gerard Dow, rather than like what the doctor is today and what he is able to do for his patient;

Received for publication May 19, 1961.

Delivered before the Convocation of the Forty-second Annual Session of The American College of Physicians, Miami Beach, Florida, May 8-12, 1961.

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and that the socialized medicine which is excoriated, is a textbook socialism quite different in direction and meaning from anything which has found a significant place in the American medical scene.

The incredible expansion of industrial and business activity in the United States, combined with a varied series of political, social, and economic forces, has altered the American standard of living, and with it, the average American's way of thinking and his status as a citizen. The doctor as a citizen has shared in these shifts and changes of attitude. He, too, has changed and along with it, his practice.

The good American doctor of today is considered by some to be one of the advanced types of human being, because in him, science is devoted to the relief of suffering. More than that, he is skeptical toward the data of his own profession, welcomes discoveries which have upset his previous hypotheses, theories, and practices, and is still animated by human sympathy and understanding.

As we scan some of the big changes in the American scene, we see that there has been a great growth in medical research and an improvement in the quality of medical education. As a result, the character of medical practice has changed. Medical education is no longer a few years of study after high school, but a lifelong study. In general, after 12 years of primary and secondary education, there are four years of college, four years of medical school, one or two years of internship, two years of military medicine, and an additional three to five years of formal training before entering the practice of medicine as a licensed practitioner, and before becoming available for admission to examination by a specialty board. It adds up to about 22 to 25 years of formal education and training. Then, the postgraduate or continuing education, lasting the rest of one's life, follows. It takes a long time to make a good doctor out of an M.D. and, if the

good doctor remains safe and effective, he must continue to study and learn in order to remain intellectually alive.

Fewer men are entering the general practice of medicine, and more and more men are preparing themselves for medical careers in one of the medical specialties. These include full-time practice, full-time teaching and research, full-time medical administration, public health work, full-time governmental services in our institutes of health, in military medicine, and in our other governmental hospitals, as well as in full-time industrial medicine. The opportunities for specialization in medicine have increased in every discipline; in fact, the opportunities for people in the special health professions have never been greater. *Specialism* has improved medical service.

Laboratory Medicine Advances: There has been a tremendous growth in laboratory medicine, an almost incredible advance in medical science and technology, and in the development of new diagnostic aids. All of these have improved the accuracy of diagnosis and aided in more rational and effective treatment.

New Weapons for Life Increase: There has been a fantastic development of new and highly effective therapeutic agents, sometimes referred to as "new weapons for life." These flowed from the research laboratories of our universities, our medical and therapeutic institutes, and our pharmaceutical industries, that are based upon scientific research. These numerous new agents have made it possible to save countless lives, relieve human suffering, prolong lives, and prevent many illnesses. All of these therapeutic agents have been developed for patients and for patients alone.

Medical Communication and News: There has been a great improvement in medical communication and in medical news through the development of more and better medical journals, more and better medical meetings, a wider use of mass

media, and the training of experienced science writers. Also, the use of the brochure, the mailing pieces, and the atlases has improved communication and shortened the lag between scientific discovery and application.

The Public Looks for Preventive Medicine: There is a growing public awareness of the possibility of preventive medicine and the need to prevent illness. The demands as well as the needs for medical care of high quality are increasing, and the utilization of all professional medical care is high.

The Rising Costs of Medical Practice: There has been a tremendous increase in the costs of maintaining a medical practice, the cost of space in medical buildings, the substantial cost of equipment that is necessary to keep pace with new advances in technology, and a substantial increase in all indirect, as well as direct, costs of carrying on a practice. This has increased the costs of professional medical care.

Hospitals Have Changed: The public is taking a hard look at their hospitals which have been developing as centers of medical practice and public health. They want modern, well equipped, well managed, adequately staffed facilities. They want more highly qualified, efficient bedside nurses, whose number has been slowly diminishing. They long for a better understanding of hospitals, of what they do and how they do it. They want to know why hospital costs keep on rising at a more rapid rate than other health services. Hospital administrators need to keep the public well informed about hospital costs, as they are related to quality and quantity of services and standards of medical care.

There is a tremendous shift in the way medical care is being distributed and in the manner it is being paid for. The organization of group clinics or group practice, the development of prepaid group practice plans, the multiplication of voluntary health insurance plans, the expansion of

public assistance and medical care assistance plans supported by government, are all growing at a fast pace.

Changes in Social Control of Physicians: All of these changes have led to a greater social control of the physician: control by legislation, medical organizations, insurance organizations, hospitals, health and welfare groups, governmental groups, and a strong public opinion. Gradually, these controls are leading to more community dominance of the profession. The direction of medical education, medical research and, hence, medical practice will come from the people, who ultimately will take what they want and what they believe will benefit them most. It will have an economic determinant. This is the area in which our profession must take the leadership; advise, guide and persuade the public, and our patients, by example, that we are practicing medicine and promoting health for their benefit.

THE CHANGING IMAGE OF THE PHYSICIAN

As we look at the canvas with its march of events in American medicine today, we see a different picture from yesterday. Let us look at another portrait—that of the changing physician.

The physician of today has forged a different image of himself from that of yesterday. Images are built upon the conception of what a doctor does and how he does it and not upon what he is called. The physician is practicing medicine today in a different way than formerly, and he will change in the future.

Every generation of physicians carves its own image, and every generation of people creates its portrait of the ideal physician. When this College was formed in 1915, one image of the physician was that of the consulting physician; another was that of the family physician or practitioner of general medicine, actively engaged in house to house practice and holding afternoon office hours.

Today, many images of the physician exist. There are still doctors who see a great variety of diseases, take care of people in their offices, in their homes, and in the hospital as general practitioners. They make the choice when special services are required.

Then there is the image of the specialist, or what is sometimes referred to as a sub-specialist. Here, the image is less clear and the figure is changing with great rapidity. These physicians obtain position, status, and recognition as specialists from their teachers, their colleagues, and their patients. They are also identified as specialists by virtue of the fact that they have met certain requirements and standards, such as Board certification and fellowship, or membership in special and distinguished societies. In short, they are recognized by *what they do*, how they do it, and by their use of expert knowledge and skill in a particular area.

Now, I believe that the ideal physician of any generation is a subtle blend of the social and economic structure of society, and of the community in which he resides. He is shaped and determined by his education, and by the technical and scientific means available at the time. Every society, every generation has required that its physician have specialized knowledge, skill, and devotion to patients. His status in society, the tasks assigned to him, the rules of conduct imposed upon him, change with each generation, but the basic image of the ideal physician has always been the same because his task in life has always been "to promote health by preventing illness and curing it." The only image of the physician that really counts in society is the one created by the patient as a result of his personal relations with his doctor. The only real image of an internist is what an internist does.

THE FUTURE

What of the future? Never has the outlook of The College and the medical pro-

fession been brighter. We have set high standards of medical practice and we strive constantly to improve them. The public is demanding more and more medical care of high quality. It is insisting that medical care be both available and accessible to all, regardless of social or economic status. It is seeking more and more ways of preventing illness and preserving health. This is the challenge that the public has created. This is the public drive for better health.

As disease is understood more thoroughly, studied and investigated more skillfully, the average sum of human suffering and sickness will be reduced in a way to make all rejoice. Many diseases familiar to our forefathers will practically disappear; the death rate from many others will fall to the vanishing point, as others take their place. New drugs, new technological advances will add years to an active, fruitful life. Public health measures, designed to prevent illness and improve health, will lessen the sorrows and brighten the lives of millions.

Research in biology as related to medicine will increase at an accelerated pace. A better understanding of life itself must emerge. Research in social medicine will be intensified. Certainly we need to know more about environmental and socioeconomic factors, as they influence the health of the people, both physical and mental. One of the great pressing problems that will command the wider attention of the profession and of the public will be concerned with mental health. In the most prosperous countries of the world, where life should be easiest, the casualties from mental causes are not lower but higher than elsewhere. Mental stress and emotional tensions are very imprecise concepts, and the criteria for well-being need better definition because the springs of well-being are more subtle than we know.

No doctor of my acquaintance is at ease with the concept of positive health. We recognize disease as a departure from a

definable norm, but how are we to define the norm of positive health? What are the criteria for an improved general welfare? We acknowledge at once, then, our difficulties in these areas, and feel that the World Health Organization may be right in reminding us that health is not a norm but a form of individual excellence. Certainly what we as physicians are seeking to know tomorrow is how to make more important contributions to human well-being, and how to promote health as something more than being alive, and not merely the absence of disease or infirmity.

As we grow, a new social order within our society will evolve, and there will be a tremendous shift in the burden of illness. We must meet the changing conditions of health. This can be done by seeking a better understanding of all factors affecting health and disease and even life itself—social, economic, and environmental.

To all the newly elected Fellows and Associates, I extend my heartiest congratulations. Fellowship in this body signifies that you have been recognized by your colleagues and peers as physicians dedicated to improving the health of people. It is a sign that you have met high standards of conduct and scholastic accomplishment. All of you will carry the banner and wear the badge of the physician. Your status as a physician will depend upon your professional relations with your patients and with the public. Your image as a physician and as a member of this College is the image that you create with your patients.

Your cup of joy will come as a reward for long, devoted, and good-natured service to medical science, medical education, medical care—all for the general welfare of man.

ACKNOWLEDGMENT

The editors acknowledge with gratitude the assistance of the following editorial consultants in reviewing manuscripts during the period October 1, 1960 to April 30, 1961.

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ANNALS of INTERNAL MEDICINE

Vol. 55 JULY 1961 No. 1

Published Monthly
by The American College of Physicians

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Executive Director

Editorial and Executive Offices
4200 Pine Street, Philadelphia 4, Pa.

Place of Publication
Prince and Lemon Streets, Lancaster, Pa.

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The ANNALS encourages the publication of papers that are excellently presented as well as scientifically sound. Papers that do not require extensive revision are more likely to be accepted promptly and to be published promptly. Authors are strongly urged to prepare manuscripts in strict accordance with *Instructions to Authors* as given in each issue on a page following *Medical News*.

Selected books and monographs will be reviewed monthly in the ANNALS. Authors and publishers wishing to submit such materials should send them to the Editor. Since it is not possible to review all books submitted, a list of all those received will be published each month in *Books: Reviewed, Noted, and Received*.

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This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscription price per annum, net postpaid: \$10.00, United States, Canada, Puerto Rico; \$7.00, in the above countries, to bona fide medical students, interns, and residents; \$12.00, in other countries. Prices for back numbers furnished upon request. Single numbers, current volume, when available, \$1.25. Checks should be drawn to the order of The American College of Physicians and remitted through the Executive Director's Office.

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EDITORIALS

New Clothes for the Lady

WHEN THE LADY OF THE HOUSE announces a little shopping trip down town "just to look around," we all know the inevitable result—a new hat, a new dress, or even a whole new outfit. Of course the old hats or dresses are not worn out, but, for reasons unfathomable to the male mind, the feminine psyche has an urge that must be met. It is met, the feminine spirit is lifted, and just as inevitably, masculine approval (feigned or real) is necessary for peace on the domestic scene. The ANNALS, with spirit lifted, has come home in a whole new outfit, clothed anew from head to toe, inside and out. The editors hope our readers will be genuinely pleased with this new appearance of an old friend.

The new format of the ANNALS has been designed for one purpose: to make the ANNALS more readable. Being more readable means being more attractive to the reader and being more easily read by him. To this end the cover has a new design, a new color, and a new quality of paper. The Lancaster Press and the editors set up ten designs in 12 colors each before the final cover was attained. Brighter and even flamboyant colors were flirted with but in the end we have chosen a cover with a simplicity of design and color that we believe will wear well. The complete table of contents is still on the outside but is on the back, where it may quickly be found merely by turning the journal over. The trim size has been changed only by an increase of one-quarter inch in width; no reader or librarian will have to change his shelf space. Inside, the principal changes are two: The pages are set in double columns and a new type face is used throughout. The double column format is easier

to read and is more efficient in the use of space. The new type face is *Baskerville*, likewise chosen for its elegant simplicity.

Indeed, the choosing of a new type face has led the editors into the world of technology and history of typography. To quote an anonymous author:

"Faces of type are like men's faces. They have their own expression; their complexion and the peculiar twists and turns of line identify them immediately to friends, to whom each is full of individuality."

Baskerville type is a "transitional" type face because it shares some of the grace and sturdiness of the old style types yet anticipates the modern in its contrasting light and heavy strokes. The letters are rounded and open and hence are very legible. This type face was designed about the year 1760 in Birmingham, England, by John Baskerville, the greatest printer and type founder of his day. Baskerville was noted for his improved methods of printing with very black ink on smooth paper, but his type face, now renowned for its beauty and excellence, was a source of derision to his fellow printers. Although his work found a better reception on the Continent and was championed by Benjamin Franklin, his printing business did not pay. On his death in 1775 his original type font was dispersed in France and is said to have been melted down for bullets during the French Revolution. But the design of his type face survived and today is widely used. This is the type that your editors have chosen for the new ANNALS.

Innumerable decisions have been involved in the design of this new format. The nature of these decisions is suggested

by the new page of *Instructions to Authors* which will be found in the back of this number and which will be printed each month. How are titles to be styled? What information about authors is to be printed? How are tables to be set up? How figure legends? What size type is to be used in footnotes, in sub-headings, in references? In the latter shall we use large and small caps for authors, upper and lower case for titles, italics for journals? Yes, for this style makes for greater readability—our major criterion for each and every decision.

And so, gentle reader, we give you the ANNALS in all her new finery. The editors are ever mindful that the woman inside the clothes, and the scientific papers inside the covers, are of the first importance—far more so than the outside appearance. Yet in the world as it is, outside appearances are important too, and as "clothes make the man" (or in this case, "the woman"), so the format makes the journal. Will you love her as you did when her old clothes once were new?

J. R. E.

The Penalty of Being a Male

AS A CARDIOLOGIST, I have been especially interested in the protection against heart attacks that "femaleness" apparently confers upon women during the childbearing years. Under the age of 40, coronary atherosclerosis is from ten to 40 times as frequent in men as in women, and coronary occlusion is virtually unknown in women under 40. In young women, when estrogen production is high, the serum lipid pattern is nonatherogenic, i.e., total cholesterol is low, and cholesterol: phospholipid and beta: alpha-lipoprotein cholesterol ratios also are low.

Some years ago, in a paper entitled "Oophorectomy and Cardiovascular Tissues," I reviewed the deleterious effects of estrogen deprivation on tissues of the body (1). I pointed out that the woman who has undergone oophorectomy develops a degree of atherosclerosis by her fiftieth year which is comparable to that customarily seen in the woman of 70, and that surgeons often include among their published reports notations that one or more of the patients died of a heart attack some 13 or 18 or 20 months after bilateral oophorectomy. Again, I wonder whether these men are aware of the relationship between these deaths and earlier removal of the ovaries.

Estrogens from either the adrenals or residual ovarian activity have been found to exert a protective influence even in postmenopausal women.

Estrogens administered to males go far toward correcting the lipoprotein spectrum from an atherogenic condition to immune healthy patterns similar to those of the premenopausal female; this is true even in men who already have suffered myocardial infarction (2). In addition to its effects on fat metabolism and on the deposition of fats in the lining of the arterial wall, estrogen also has been found to promote the effects of heparin when administered to persons who otherwise are heparin-resistant.

Let us explore the dubious advantages of being a male. Actually, the advantage at the time of conception is in favor of the male; for each 100 females conceived, 120 to 150 males are conceived. However, from the time of fertilization onward, the mortality rates before birth are higher for the male than for the female fetus. On the average, intrauterine deaths are 50% higher for the male fetus. In the United States the ratio at birth is 105 males to 100 females. Birth injuries claim 53% more males than females among full term babies, 80% more males among premature babies.

Among full term babies in the four weeks after birth, male deaths exceed the female deaths by more than 40%; within the first year of life, three boy babies die for every two girl babies. When we examine the mortality rates of boys and girls during childhood and throughout the teens, we find that in the five- to nine-year bracket, male mortality exceeds female mortality by 44%; in the five years from ten through 14, male mortality exceeds that of the female by 70%; and in the years from 15 to 19, the difference has climbed to 145%! Although differences in habits and activities may enter into this difference, they cannot account for the huge advantage in favor of the females.

In the crucial age range from 40 to 74, heart diseases kill twice as many males in the United States as females: 872 males per 100,000, compared with 437 females per 100,000. In other advanced countries, the male-to-female mortality rate may vary, but the males always die sooner than the females. However, in the Netherlands, the over-all rate and differences between the sexes are considerably reduced: 315 male cardiovascular deaths occur for each 220 female deaths. With the passage of time, life expectancy of the male has not kept pace with that of the female (3). Whereas in 1850 life expectancy of the male in the United States was 34 years and that of the female 36 years, a difference of only two years, by 1958 life expectancy of the male had increased to 68 years and that of the female to 76 years, a difference of eight years. Life expectancy in England and Wales is comparable. Inasmuch as women are no more resistant than are men to infectious or contagious diseases, this gain is primarily due to resistance of the women to degenerative diseases. The effects of hypertension and obesity are somewhat less severe in women than in men. As the blood pressure of the female normally is slightly higher than that of the male, her vasculature may be designed to accommodate

higher pressures. And according to statisticians of the Metropolitan Life Insurance Company, women aged 15 to 39 years who weigh 20% more than the average have a mortality rate 15% higher than the average for their sex, whereas in a comparable group of overweight men, the mortality rate is 24% higher (4).

In passing it may be noted that males, in addition to being weaker and less durable than females, suffer from certain other disadvantages. Males lag behind in verbal and linguistic abilities. Males are slower to respond to physical or mental stimuli. Males are more aggressive but their aggressiveness or lack of caution makes them more accident prone. Men are less able than women to handle the severe shocks of daily life. Men commit suicide two to five times more frequently than do women.

But for those members of both sexes who so far successfully avoid these paramedical pitfalls of life as to become targets for the degenerative diseases, let us consider the interrelationship between atherosclerosis and the female hormones. Most physicians undoubtedly are aware that a sex difference in atherogenesis exists, but few realize that atherosclerosis is present as universally in young men as is the case. A study by the Armed Forces Pathological Institute (5) shows that 70% of young airmen killed in air crashes have moderate amounts of atherosclerosis, despite the fact that they are between 18 and 29 years of age (average 22 years). In a number of instances, the crashes are believed to have resulted from myocardial infarction. In women within the same age range, even during pregnancy when circulating levels of blood fats are markedly elevated, atherosclerosis and myocardial infarction are extremely rare. Apparently, women are able to handle blood fats more efficiently than men can. Myocardial infarction is rare in women throughout the childbearing years, but becomes more frequent after normal or surgical menopause. Women with myocardial

infarction have a much lower level of urinary estrogens than women who have not suffered myocardial infarction (6).

Male sex hormones appear to be detrimental insofar as myocardial infarction is concerned (7): castrated men are not as prone to develop myocardial infarction as are normal males.

In an experimental study in progress for some years in our department, we have approached the problem of atherogenesis in several ways (8, 9). We have studied closely matched pairs of women who have suffered myocardial infarction and have found that the administration of small amounts of estrogen to one member of each pair apparently prolongs the life of the treated patient. Men with myocardial infarction and elevated blood lipids have been started on small doses of estrogens, and the amounts have been increased stepwise until breast tenderness or other evidence of feminization, serum cholesterol, and cholesterol: phospholipid ratios were lowered to the normal range. Severe atherosclerosis has been developed experimentally in beagles by interference with thyroid function and the administration of an atherogenic diet. Administration of estrogen caused regression of the atherosclerotic lesions despite continuance of the atherogenic regimen. If estrogen was administered concurrently with the atherogenic regimen, atherosclerosis was prevented.

We also have found estrogen to be useful in instances where patients maintained on heparin have become resistant to the antilipemic and anticoagulant effects of the drug. Temporary treatment (two weeks) with estrogens has served to re-establish heparin sensitivity.

We see, therefore, that from conception forward, throughout life, women have a definite advantage over men. If we males wish to avail ourselves of some of this

advantage, we must borrow the protective factor that is the normal birthright of the so-called weaker sex. Perhaps the administration of conjugated estrogen in a small dose that does not produce breast changes or loss of libido should be considered for every male patient found to have an abnormal distribution of the fat pattern plus early clinical findings of atherosclerosis. If you can't lick 'em, join 'em!

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The Question of Hypertension

IN THIS ISSUE OF THE ANNALS are found three provocative papers dealing with essential hypertension. Each contributor raises a different question; each answer is itself subject to question. Perhaps more than anything else, these manuscripts serve to illustrate that it is a legitimate function to arouse curiosity, although not always to satisfy it.

Sir Robert Platt provokes us in a most interesting fashion with his "tentative" conclusion that essential hypertension is a hereditary disorder. But has he distinguished genetic inheritance clearly from what may be merely a familial concentration? This is a vital point. The appropriateness of a continuing search for a primary metabolic or biochemical derangement, as opposed to a continuing examination of social, environmental, and psychological influences, depends upon the answer. Is he correct that malignant hypertension is the natural consequence of a very high blood pressure, or does he ignore the possibility that the hypertensive person is more prone to succumb to a process of a separate or superimposed nature? One's therapeutic approach will rest upon the answer. Should Sir Robert have re-evaluated the data of Pickering, made up predominantly of single blood pressure readings? Upon the validity of the data depends the answer.

Genest and his associates submit a fascinating manuscript suggesting that there are definite endocrinological abnormalities in patients with hypertension, both benign and malignant. One notes the question mark placed in the title of their initial manuscript of 1956, the results then being "based on a biological determination of a purified aldosterone fraction obtained after two successive chromatographic purifications of the crude, neutral extract of acidified urine." A more specific physicochemi-

cal determination is now employed. Are the methods sufficiently exact to measure aldosterone excretion accurately, and is the difference between a daily output of 4 μ g for normals and 12 μ g for essential hypertensives significant? Upon the method, in this instance, depends the answer. Is a corticosteroid disturbance associated with the cause of the disorder, or is it a response to an unrecognized degree of renal damage which secondarily provokes the adrenal cortex? Again, upon one's interpretation depends the answer. As Genest points out, the studies of Laragh on the secretion of aldosterone in uncomplicated patients suggest normal rates; hence further clarification is needed. Both Laragh and Genest have opened new vistas with their observations, indicating that angiotensin infusions can and do produce an increased elaboration and excretion of aldosterone.

Finally, there is this writer's preliminary suggestion that an antithyroid drug may exert secondary influences upon the vascular tissues affected by malignant hypertension in man. Can one always be certain of the diagnosis on clinical grounds alone? Is enough known about the evolution of this disorder to eliminate coincidence in so small a series? Here the answer depends on confirmation and extension of the theory.

There is probably a place for the preliminary, the provocative, and even the controversial. One can be reasonably certain that no one of the authors of these studies would regard his contribution as a final answer to the problem. Yet each, in his way, has submitted some new evidence or provoked some new inquiry.

The ultimate solutions depend on asking the right questions.

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BOOKS

Book Reviews

Congenital Malformations of the Heart. 2nd (Rev.) Ed., in two volumes. By HELEN B. TAUSSIG, M.D. Vol. I: 204 pages; Vol. II: 1,049 pages. Both 27 × 18 cm. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1960. Prices: Vol. I, \$4.75; Vol. II, \$17.50.

The first edition of *Congenital Malformations of the Heart*, which was published in 1948, consisted of one volume with 618 pages. The author stated that it was designed for reference. Its clinical orientation made it highly popular with the rapidly increasing numbers of those interested in the subject. It was useful not only for reference but, because of the orderly, lucid, detailed presentation of data and the numerous clear figures and diagrams, it made an excellent textbook.

In the present edition, the author has undertaken the task of preserving the valuable material and features of the first, integrating into the text, with necessary modifications, the great new store of material that has accumulated since 1948. A few new chapters, numerous new illustrations, and a "Visual Index," provided to exhibit the essential features of the malformations, have been added. All this has more than doubled the number of pages and justifies the two volumes. Volume I, under the subtitle "General Considerations," covers Part I of the first edition, previously entitled "Physiology of the Malformed Heart and Diagnostic Principles," to which a new chapter dealing with angiography, aortography, and cardiac catheterization has been added. Part IV, previously entitled "Therapeutic Measures," is now called "Medical Care," doubtless in deference to the tremendous advances in surgical therapy since 1948. Volume II, subtitled "Specific Malformations," is divided into four major categories of classification (somewhat changed from the first edition) and 30 chapters, including several new chapters dealing with such subjects as pulmonary hypertension, the Taussig-Bing malformation, defective development of the right ventricle with an intact ventricular septum, and aortic septal defect. Comparison of the two editions furnishes a clear record of the amazing progress made in 12 years.

The mode of presentation of the various specific malformations follows that of the first edition. Thus, in Chapter VI, which deals with the tetralogy of Fallot, after an introductory discussion including historical data, the following headings appear: "Nature of the Malformation," "Course of the Circulation" (both in fetal life and after birth), "Physiology of the Malformation," "Clinical Findings," "Cardiac Findings," "X-ray and Fluoroscopic Findings," "Electrocardiographic Findings," "Special Tests," "Diagnosis," "Differential Diagnosis," "Commonly Associated Malformations," "Complications," "Treatment" (including indications for various types of surgical treatment and their results), "Prognosis," "Summary," and "References." In this chapter alone there are 25 figures and six diagrams with complete explanatory legends. In some chapters, illustrative case reports are included.

The present edition, as was the first, is highly useful for purposes of reference. The index has been carefully prepared. The summaries and references at the ends of chapters are also convenient to use. Its length may make it seem more formidable as a textbook, but there is a lot more to be learned now than there was 12 years ago. The author admits the presence of repetition, but it could scarcely have been avoided without numerous cross references. The repetition is doubtless an advantage from the pedagogic point of view and makes reference more convenient, even though it adds to length.

Dr. Taussig deals with her subject from the viewpoint of a seasoned clinician who utilizes clinical methods to their fullest extent, and who regards them as the keys to diagnosis and the bases for the choice of definitive procedures that may be required to solve the problems of the patient under consideration. In fact, she warns against the substitution of a battery of laboratory tests for careful clinical study which may render many such tests unnecessary. She, like all sound clinicians, recognizes among the various clinical procedures the value of auscultation, and has carefully described the findings and the changes that may take place due to the various malformations and their combinations. Her description of the continuous bruit

heard over the lung fields in truncus arteriosus is an excellent example of the results of careful study. But perhaps she might yet find more precise terms for heart sounds than "weak," "of poor quality," or "forceful," and a more accurate one than "split pulmonic second sound." By an early diastolic murmur she appears to mean one that begins in early diastole irrespective of its duration, rather than one limited to early diastole. Although she can scarcely be criticized for following the bad precedent set by so distinguished an observer as Carey Coombs, who referred to two different murmurs as "mid-diastolic," it is time to abandon the application of this term to murmurs such as those produced by mitral stenosis, reserving it for murmurs fairly well limited to the mid-diastolic period. She states that gallop rhythm is a sign of a poorly functioning or failing heart, but if she wishes to limit the use of the term to such cases, she has not informed us how to differentiate such sounds from other sounds with apparently identical characteristics which are heard in a great variety of circumstances over apparently vigorously functioning hearts when large waves of ventricular filling occur. There are other statements about heart sounds concerning which one might be captious, including those on the presystolic gallop, presumably loudest at the aortic area in coarctation of the aorta when hypertension is severe, and those on sound patterns in complete heart block. But the area in which one must agree with the author is large and the area of disagreement comparatively small.

In her characteristically forthright manner, Dr. Taussig states that she will not discuss matters with which she has not had personal experience. Consequently, those who wish to acquaint themselves with current applications of dye dilution curves, cine-angiography, and intracardiac phonocardiography to the problems of congenital malformations will have to seek this knowledge elsewhere. Selective angiography is not presented as fully as enthusiasts for this procedure might like. But the other special diagnostic procedures now employed appear to have full coverage. The discussions of fluoroscopic findings are outstanding. Like all good cardiac fluoroscopists who know what to look for and when to look for it, she obtains more information from fluoroscopy than from films, although obviously the latter are frequently needed.

A change from the first edition, in which only the Einthoven limb leads were shown in the electrocardiographic illustrations, has been

the use of the "twelve lead electrocardiogram," sometimes with supplementary right precordial leads, although there is little if any reference in the text to the augmented extremity leads. Vectorcardiography is mentioned briefly; there is only one reference to it in the index. Those who have misgivings concerning the unipolarity of unipolar leads or are impressed by what they regard as certain inherent limitations of electrocardiography may not be completely prepared to accept her statement that the unipolar precordial leads indicate the relative thickness of the two ventricles, that V_1 and V_{3R} give evidence of the amount of work required of the right ventricle, and that V_5 and V_6 give the same evidence for the left ventricle. These views obviously permit considerable latitude in interpretation of electrocardiograms beyond that permitted themselves by some workers. In any event, the author is convinced that the unipolar precordial leads have been found highly useful. Their development is attributed by Dr. Taussig to W. H. Craib and the late F. N. Wilson, although usually the unipolar idea has been credited to Wilson and his co-workers alone, based upon their applications of Einthoven's assumptions.

This is a book which should be readily available to all undergraduate medical students, hospital interns, and residents. It can be employed profitably as a reference by general practitioners, pediatricists, and internists when they encounter puzzling situations in which a congenital malformation of the heart may be concerned. Experts in cardiology will not need to be told to read it. They can scarcely afford not to be familiar with Dr. Taussig's ideas and opinions.

CHARLES C. WOLFERTH, M.D.

Management of Hypertensive Diseases. By JOSEPH C. EDWARDS, M.D., with a foreword by PAUL DUDLEY WHITE, M.D. 439 pages; 25.5 × 17.4 cm. The C. V. Mosby Company, St. Louis, Mo., 1960. Price, \$15.00.

The author has used well his extensive experience to present in easily readable fashion a method of studying the patient with hypertension. Dr. Edwards might well have injected more of his own opinions into this treatise, but he does supply a very comprehensive bibliography which should be helpful to those working in the field. However, the book has much to offer to the student and the general practitioner, as well as the specialist.

Following a definition of hypertension and a discussion of factors which influence the

maintenance of blood pressure, the author reviews the differences between essential, neurogenic, and accelerated or malignant hypertension. Important features of evaluation of the patient are well presented; discussion of examination of the ocular fundi is particularly good.

Chapters concerning heart disease and electrocardiographic abnormalities associated with hypertension perhaps present more detail than is necessary, but they are nevertheless instructive.

Proper recognition is given to the special problem of hypertension associated with pregnancy, and a plan of study and treatment is offered in detail. Surgically curable forms of hypertension are discussed with a planned approach for diagnosing important renal and adrenal abnormalities, as well as other specific etiologic factors. The book excels in being current with respect to the drug therapy of hypertension; new agents still under investigation are included with those long established for their effectiveness. The importance of the pharmacologic principles which underlie the mode of action of these drugs is emphasized and contributes to the formulation of a good therapeutic plan.

This book is clinically oriented, as the title suggests, and thus will appeal most to those facing the problems of the management of patients.

ALFRED M. SELLERS, M.D.

Clinical Applications of Cardiopulmonary Physiology. By M. HENRY WILLIAMS, JR., M.D. 233 pages; 24.5 x 16 cm. Paul B. Hoeber, Inc., New York, 1960. Price, \$7.50.

In this short, concise, well-written book Dr. Williams briefly reviews normal cardiopulmonary physiology and discusses the techniques used in the determination of normal and abnormal physiologic states, together with their indications, contraindications, and interpretations. The various congenital and acquired pulmonary disorders are discussed individually, with emphasis on the associated states, and in each instance the author concludes with remarks on the proper course of treatment and how it works.

The book is attractively printed, has an excellent, current bibliography and an adequate index, and is easy to read.

In his preface Dr. Williams states, "It is the intent of this book to outline normal pulmonary physiology, to point out the areas that may be assessed by physiologic techniques, and to indicate the bearing that such studies have on

the diagnosis, evaluation, and treatment of patients with cardiopulmonary disease." In my opinion Dr. Williams has accomplished his purpose admirably, to the benefit of medical students, house staff, and physicians and surgeons who are not in daily contact with patients who have cardiopulmonary disorders.

JOHN HELWIG, JR., M.D.

Current Therapy—1961. Edited by HOWARD F. CONN, M.D.; Consulting Editors: GEORGE E. BURCH, M. EDWARD DAVID, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, CLARENCE S. LIVINGOOD, PERRIN H. LONG, H. HOUSTON MERRITT, WALTER L. PALMER, HOBART A. REIMANN, RALPH WAYNE RUNDLES, and ROBERT H. WILLIAMS. 806 pages; 27.5 x 20.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$12.50.

That new editions of this therapeutic guide have appeared for 13 consecutive years proves its popularity. Again, Dr. Conn and his 12 consulting editors have gathered essays on the treatment of specific diseases, syndromes, and symptom-states from physicians located at all compass points in the United States. These essays give reliable and specific instructions for the physician, and steer courses between and clear of both traditional (but useless) nostrums and the latest wrinkles and gimmicks not yet widely tested.

Although the quality of this volume again justifies its appearance, some minor flaws appear in it. The table of "Laboratory Values of Clinical Importance" in the end papers has not been critically examined. The daily urinary excretion of creatinine is given as 1.0 to 1.6 g; though this range may be representative of creatinine excretion by adults of average size, it would be more usefully expressed in terms of grams (or milligrams) per unit of body weight, so as to include the range for children. The range of daily urinary calcium excretion is given as 0.1 to 0.7 g; very few adults excrete more than 0.25 g per day, and values above 0.3 g can almost invariably be taken to represent clearly pathologic hypercalciuria. Values for ammonia excretion in the urine, given without reference to body weight, urinary pH, and plasma acid-base equilibrium are virtually useless. And can an entry for cardiac output be justified as having "clinical importance"?

Some essays are diffusely focused and do not justify their appearance in this type of book; the one on "General Nutritional Deficiency," though not inaccurate, has this weakness. Occasionally, too, an antique point of view ap-

pears—for example, the “acidosis (of uremia) is the result of excessive retention of anions.” This interpretation, recently laid to rest by Halvor Christiansen and William Schwartz, would lead us to expect that patients with idiopathic hypoparathyroidism (and phosphate “retention”) would show metabolic acidosis, and they do not. Another traditional view, of doubtful value, is that exercise is useful in the treatment of obesity.

In the article on “Sprue (The Malabsorption Syndromes),” the gluten-free diet, an almost invaluable treatment for one-third to one-half of patients with idiopathic steatorrhea, is mentioned briefly and not described for practical use. The physician who wishes to prescribe this diet must look elsewhere for adequate guidance. Furthermore, a frequent and disabling complication of idiopathic steatorrhea, namely osteomalacia, will not be properly treated with the regimen described, if the patient does not respond to a gluten-free diet. And compounding this flaw, the article on “Rickets and Vitamin D Deficiency” does not describe the use of large doses of vitamin D for osteomalacia of this etiology.

These examples of several types of flaws in this book are not cited to infer that it is grossly defective. But its potential readers should know that it is not an infallible guide. As a remedy, the editors might allow each contributor to add one or two appropriate and recent references to his article so that physicians using the book will be directed to alternative points of view or to information on details of treatment which cannot be included in such a comprehensive text.

These essays can all be read for instruction but few can be read for delight. One striking exception is that by Kligman on “Contact Dermatitis,” and only a quotation will illustrate:

“The active ingredient in wet therapy is that most vital of all substances, water. Water cools and cleanses. It relieves itching, temporarily at least. . . . As a rule, some agent is put into the water to satisfy the psychologic needs of both practitioner and patient. It is foolhardy to combat tradition and insist on a pure water approach. To be sure, some pharmacologic rationalization is available to justify the incorporation of ‘active’ ingredients in the water; accordingly, one speaks of antioxidants, keratolytics, germicides, astringents, etc. In reality, however, these substances merely possess some sensory effect which unmistakably signifies activity; they stain, sting, or stink.”

Give us more Kligmans who are not afraid to swing their fists in public.

One of the most valuable sections in this

book is that devoted to poisoning; this feature alone is worth the price. A compilation of common poisons includes short and precise instructions for the treatment appropriate to each case. Following this section is a listing of Poison Control Centers in the United States and Canada from which physicians may get help. The section is completed with lists of potentially poisonous substances in 48 household items and several hundred commercial products (identified by trade names).

Current Therapy is a valuable guide, when its occasional weaknesses are discounted, and has no peer among medical textbooks of this type. Because true advances in therapy develop relatively slowly, physicians need feel no compulsion to buy this book each year. If they do, however, and consult it often, they will have spent their money to the advantage of their patients and themselves.

EDWARD J. HUTH, M.D.

Medical Entomology. 5th Ed. By WILLIAM B. HERMS, SC.D., revised by MAURICE T. JAMES, PH.D. 616 pages; 24 × 16 cm. The Macmillan Company, New York, 1961. Price, \$12.50.

This book first appeared in 1915 under the title *Medical and Veterinary Entomology*. A fifth edition in less than 50 years is adequate measure of its acceptance and usefulness, and of the growth of this area. Its subject matter ranges from those bits of information that may be needed to understand and manage the stings, bites, and blisters, including some of the intestinal disturbances that mar vacation time, to vector control or eradication with all of its ramifications into ecology, economics, conservation, and politics. One might wish for a fuller treatment of the abuses of insecticides and the development of resistance by flies and mosquitoes. This phenomenon parallels in time the altered response of infectious agents to chemotherapy. Perhaps the basic mechanisms are the same, although undoubtedly an adequate discussion would itself require space equal to this book. As it is, the book can be recommended to internists, to laboratory directors, and to students who may be planning a career in this area.

HERBERT L. RATCLIFFE, SC.D.

Haematology. By R. B. THOMPSON, M.D., F.R.C.P. 306 pages; 22.3 × 14 cm. Pitman Medical Publishing Co., Ltd.; J. B. Lippincott, Philadelphia, exclusive U. S. agents, 1961. Price, \$6.00.

This book attempts to condense the field of hematology for presentation to interested medi-

cal students and practitioners of medicine. Almost every disease seen in present-day hematology is mentioned, and several sections of the book, such as the one on hemolytic anemias, appear to be adequate for their intended purpose.

On the whole, however, the book is disappointing in its organization and scope. Some areas, such as the hemoglobinopathies and the use of radioactive isotopes in diagnosis, are so sketchily covered as to be of no real value. I do not believe the book will prove to be of use in the teaching of hematology to medical students, nor can it be recommended to internists wishing to review the status of present-day concepts of English and American hematology.

ARTHUR J. WEISS, M.D.

Clinical Cardiopulmonary Physiology. 2nd Ed.

Editor-in-Chief: BURGESS L. GORDON, M.D.;

Editorial Board: ROSS C. KORY, M.D., ALBERT

H. ANDREWS, JR., M.D., JOHN F. BRIGGS, M.D.,

BENJAMIN M. GASUL, M.D., EDWIN R. LEVINE,

M.D., and JOHN J. SAMPSON, M.D. 1,001 pages;

28 × 20 cm. Grune & Stratton, Inc., New York and London, 1961. Price, \$28.50.

More than half of the 1,001 pages and 63 chapters in this book, written by different authors, treat the pathological physiology of respiration, the remainder being concerned with the circulation. The personal experiences of the authors in fields in which they are well versed is apparent throughout. Practically all of the chapters are good sources of information. Several of the articles are, by virtue of their critical analysis of the literature or by the inclusion of original material, unique. While all of the authors strive to be impartial, and most of them succeed in documenting their statements, it is impossible to avoid some authoritarianism in such a treatise, and hence research workers in this field must inevitably turn to the original literature.

This book should prove helpful to those who wish to study the pathological physiology of the heart and lungs, but do not have the library resources or the time to wade through the growing documentary literature. Each chapter is illustrated with graphs, diagrams, X rays, and tables. There is a bibliography at the end of each chapter. Although the book is rather bulky, the pages and the print are large and are easy to read. Each author has completed his chapter in such a way that the reader may turn to any topic and find intelligible and comprehensive coverage.

In summary, this book is a description of the application of physiology to the diagnosis and treatment of circulatory and respiratory diseases. It deserves a place in libraries used by graduate physicians and by third or fourth-year students, who will want to consult many parts of it concerning the pathophysiology of the heart and lungs.

ARTHUR B. DuBOIS, M.D.

This volume, sponsored by the American College of Chest Physicians and edited by Dr. Burgess L. Gordon, with contributions of individual sections by authors who are recognized experts in their fields, is a well-written and well-printed book, with excellent illustrations and excellent bibliographies.

Starting with a superb chapter on the history of cardiovascular physiology, the book in successive chapters reviews the normal and abnormal anatomy of the heart; normal and abnormal physiologic states; and the various specialized techniques, such as auscultation, electrocardiography, phonocardiography, angiography, right and left heart catheterization, and other specialized methods used in the evaluation of patients with normal and abnormal physiologic states. Specific cardiovascular diseases, including diseases of the myocardium, acquired and congenital valvular disease, and other types of congenital heart disease are well covered.

This book is the best single source of this type of information that is known to this reviewer. It suffers somewhat from multiple authorship; there is a fair degree of duplication throughout the book and some degree of unevenness of coverage. For example, the chapter on cardiac catheterization and indicator dilution curves takes as much space as the chapter on kinetocardiography.

In spite of these minor drawbacks, this book can be well recommended as a reference for all physicians interested in normal and abnormal cardiopulmonary physiologic states and the many specialized techniques for their evaluation.

JOHN HELWIG, JR., M.D.

Cardiovascular Dynamics. 2nd Ed. By ROBERT

F. RUSHMER, M.D. 503 pages; 26 × 17 cm.

W. B. Saunders Company, Philadelphia and

London, 1961. Price, \$12.50.

This book is an extensive revision of a book by the same author entitled *Cardiac Diagnosis: A Physiologic Approach*. It concentrates upon the application of fundamental physical prin-

ciples to the structure, function, and control of the heart and the circulation in health and in disease. The text is direct and forceful, and the illustrations are exceptionally well designed and utilized. The beginner will learn, remember, and understand this solid introduction to the complexities of cardiovascular dynamics. The most experienced clinical or investigative cardiologist will find fixed beliefs challenged with new ideas, or with new correlations of old ideas, in this intensive and valuable review. For anyone who wishes a concise explanation of the logic and significance of modern technical developments in the field, the book is a good reference.

This is an excellent book. It should be of great interest to medical students, investigators, and clinicians.

CALVIN F. KAY, M.D.

Psychophysiological Aspects of Space Flight.

Edited by Lt. Col. BERNARD E. FLAHERTY, USAF (MC). 393 pages; 24 × 16.5 cm. Columbia University Press, New York, 1961. Price, \$10.00.

The 28 papers in this volume were presented at the Symposium on Psychophysiological Aspects of Space Flight, held at the Air Force School of Aviation Medicine in May, 1960. The goal of the conference, as stated in a preface by General Otis Benson, was to survey present knowledge of man's behavioral capabilities in space and to recommend directions for future research. While the topics covered are broadly related to behavioral problems, only a few of them involve psychophysiology. A more descriptive title would thus have been *Psychological and Physiological Aspects of Space Flight*.

It is appropriate that the first questions raised concern whether man should go into space and what he should do once he is there. These questions are clearly dealt with by Dr. Ernst Stuhlinger, who feels that "man will be guided and driven into space by the same motives which drove him to the poles of the earth some 60 years ago." While this answer neglects the economic and other logical arguments which may be raised, it states a truth. Man will explore space because it's the "nature of the beast." Since human history indicates that man is driven to explore, pleas that he shouldn't will not stop him.

Both Stuhlinger's paper and that of Donlan and Heberlig provide lucid discussions of the technical problems of space flight; they include descriptions of the Mercury capsule and test program which will be of special interest. Another paper, by Voas, gives an excellent account of the Mercury training program. First-hand accounts of personal experiences in "space-analogous" situations are given by Simons and co-workers, and by Kittinger. These complement the thorough on-the-ground simulated space flights reported by Steinkamp and Hauty.

Another group of papers deals with issues that, although not specific for space flight, are basic to space medicine. These include the "Neurophysiology of Stress," by Magoun, "Neuroendocrine Aspects of Stress," by Applezweig, "Physiological Cycling," by Kleitman, "Circadian Rhythms," by Halberg, and "Physiological Data Acquisition," by Burch and Childers. A series of papers on human reliability includes discussions of sensory overloading, by Miller; sensory deprivation, by Cameron and his colleagues and by Holt and Goldberger; isolation, by Lilly and Shurley; and skill maintenance, by Fitts.

Perhaps the most imaginative contribution is that of Kline and Clynes, who discuss "Drugs, Space, and Cybernetics." They point out that the attempt to enter space by taking along the milieu of Earth is "dangerous temporizing." Man should use his creative intelligence, they feel, to control his own evolution and to adapt himself to a space environment, perhaps through the development of "Cyborgs"—artificial homeostatic systems using chemical or electronic means to extend the organism's own self-regulatory mechanisms. For example, more efficient methods than breathing might be devised for the exchange of oxygen and carbon dioxide. Applications of this principle to such problems as wakefulness, hypothermia, fluid exchange, cardiovascular control, and radiation are considered.

While their styles are uneven, these and the other papers in this volume are mostly well-written and readable. Most of them are written by authorities in their area, although few authors seek to treat their subjects exhaustively. The book, therefore, provides an excellent introduction to a variety of issues whose importance will increase in the years to come. It should be of interest to most physicians.

GEORGE E. RUFF, M.D.

Book Notices

Pathogenesis and Therapy in Edema. Proceedings of the 6th International Congress of Internal Medicine, Basel, 1960. Edited by A. GIGON and H. LUDWIG. 206 pages; 22 × 15.2 cm. Benno Schwabe & Co., Basel-Stuttgart, 1960. Available in the U. S. solely through Intercontinental Medical Book Corp., New York 16, N. Y. Price, \$5.00 (paper bound).

The papers which were presented to the Congress have been published in the languages (English, French, and German) in which they were originally given; but the nonlinguistic physician interested in this subject should not feel deprived, for the majority of the published work has appeared elsewhere in reasonably accessible form.

Some subjects represent review articles; others are represented only by very short abstracts. The main value of this volume is its bibliography, incomplete though it is, of the European literature pertaining to aldosterone, edematous states, diuretics, and, though somewhat off the main track, interstitial nephritis.

GEORGE D. WEBSTER, M.D.

Medical Almanac, 1961-62. Compiled by PETER S. NAGAN. 528 pages; 19.5 × 13.3 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$5.00 (paper bound).

In this skeptical age, almanacs have dropped prophecies. Mr. Nagan's *Almanac* simply presents facts and data useful to many people in medicine. He has brought together lists of medical publications (with addresses, editors, circulation figures, etc.), dates of meetings, and tables of statistics (vital and financial), among other data. Short articles describe the specialty boards, medical agencies in government, and medical schools. One section provides a useful guide for

the preparation of income tax returns. The only useless section is that brief one which simply lists 12 titles under the heading, "Some Leading Foreign Medical Journals."

This novel book should be especially helpful to medical administrators and public relations "experts" in medical organizations, because it brings together information otherwise scattered among many sources. All hospital libraries should have a copy.

EDWARD J. HUTH, M.D.

The Study of Influenza. A Translation from the Russian. Public Health Service Publication #792. By V. M. ZHDANOV, V. D. SOLOV'EV, and F. G. EPSHTEIN. 939 pages; 26 × 21 cm. Prepared and distributed by the U. S. Department of Health, Education, and Welfare, Russian Scientific Translation Program, National Institutes of Health, Bethesda, 14, Md., 1960. Distributed at no charge to medical and other academic institutions and research organizations.

Written by three Soviet investigators of influenza, this long monograph is a summary of research in this disease with emphasis on Soviet contributions. Most of the work discussed has been done since World War II, but pertinent citations are taken from the older literature.

Among the topics taken up are the nature of the influenza viruses, the pathogenetic and immunologic reactions of the disease, the clinical behavior and epidemiology of influenza, and diagnosis, treatment, and prophylaxis.

This translation has been prepared in typescript, satisfactorily reproduced, but the half-tone illustrations are of poor quality.

EDWARD J. HUTH, M.D.

Books Recently Received

Books recently received are acknowledged in the following section. So far as is practicable those of special interest are reviewed, but it is not possible to discuss them all.

- Adrenergic Mechanisms. Ciba Foundation Symposium.* Editor for the British Pharmacological Society: J. R. VANE, B.Sc., D.Phil.; Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and MAEVE O'CONNOR, B.A. 632 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1960. Price, \$12.50.
- Advances in Blood Grouping.* By ALEXANDER S. WIENER, M.D., F.A.C.P. 549 pages; 26 × 17.5 cm. Grune & Stratton, New York and London, 1961. Price, \$11.00.
- Annual Review of Pharmacology. Vol. 1, 1961.* Edited by WINDSOR C. CUTTING, M.D.; Associate Editors: ROBERT H. DREISBACH, M.D., and HENRY W. ELLIOTT, M.D. Annual Reviews, Inc., Palo Alto, Calif., 1961.
- An Atlas of Acquired Diseases of the Heart and Great Vessels. Vol. I: Diseases of the Valves and Pericardium; Vol. II: Coronary Arterial Disease, Systemic Hypertension, Myocardopathies, The Heart in Systemic Disease, and Cor Pulmonale, Acute and Chronic; Vol. III: Diseases of the Great Vessels.* By JESSE E. EDWARDS, M.D. 1,041 pages, plus indices; 28 × 21 cm. (each volume). W. B. Saunders Company, Philadelphia, 1961. Price, \$70.00 (three volumes).
- An Atlas of Bronchoscopy.* By A. HUZLY, M.D. 95 pages; 25 × 17.5 cm. Grune & Stratton, New York and London, 1961. Price, \$12.50.
- Cardiopericardiomyopexy: New Surgical Treatment for Heart Diseases.* By AARON N. GORELIK, in collaboration with Prof. CAMILLE LIAN, Prof. LOUIS THIEBLAT, Dr. MENDEL JACOBI, Dr. RALPH RICCIARDI, and Dr. MADELEINE HASCHER. 176 pages; 21.5 × 14 cm. The Myopexy Association of the State of New York, 1960.
- Chest Pain: Systematic Differentiation and Treatment.* By NATHANIEL E. REICH, M.D., and RUDOLPH E. FREMONT, M.D. 366 pages; 23.5 × 16 cm. The Macmillan Company, New York, 1961. Price, \$9.00.
- Clinical Disturbances of Renal Function.* By ABRAHAM G. WHITE, M.D. 468 pages; 25 × 17 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$10.50.
- Diagnostik: Kunst und Lehre zu Erkennen. Das Röntgenbild des Herzens.* By Dr. D. ROUTIER, Dr. P. VON DESCHWANDEN, and Dr. W. O. ZÜRCHER. 69 pages; 14 × 10.5 cm. Georg Thieme Verlag, Stuttgart, 1961. Price, \$1.45 (paper bound).
- The Dyslipidoses.* By RAÚL FLEISCHMAJER, M.D. with a foreword by MARION B. SULZBERGER, M.D. 509 pages; 23.5 × 16 cm. Charles C Thomas, Springfield, Ill., 1960. Price, \$16.00.
- Essential Hypertension: An International Symposium Held in Berne, June 7-10, 1960, under the Sponsorship of the Ciba Foundation.* F. C. REUBI, Chairman; K. D. BOCK and P. T. COTTIER, Editors. 392 pages; 21.3 × 14.3 cm. Springer-Verlag, Berlin, 1960. Price, DM 33.80.
- European Standards for Drinking-Water.* 52 pages; 24 × 16 cm. Published by the World Health Organization, Geneva, 1961. Price, 60¢ per copy (paper bound).
- Handbook of Surgery.* Edited by JOHN L. WILSON, M.D., and JOSEPH J. McDONALD, M.D. 644 pages; 18 × 10 cm. Lange Medical Publications, Los Altos, Calif., 1960. Price, \$4.00.
- Intra-abdominal Crises.* By KENNETH D. KEELE, M.D., F.R.C.P., and NORMAN M. MATHESON, F.R.C.S., M.R.C.P., F.A.C.S. 397 pages; 21.3 × 14 cm. Butterworth, Inc., Washington, D. C., 1961. Price, \$10.00.
- A Manual of Cutaneous Medicine.* By DONALD M. PILLSBURY, M.D., WALTER B. SHELLEY, M.D., and ALBERT M. KLIGMAN, M.D. 430 pages; 24 × 16 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$9.50.
- Medical Almanac, 1961-62.* Compiled by PETER S. NAGAN. 528 pages; 19.5 × 13.3 cm. W. B. Saunders Company, Philadelphia, 1961. Price, \$5.00 (paper bound).
- Metabolic Effects of Adrenal Hormones. Ciba Foundation Study Group No. 6.* Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and MAEVE O'CONNOR, B.A. 109 pages; 19 × 12.5 cm. Little, Brown and Company, Boston, 1960.
- Neurology Workshop. Vol. I: Scalp, Skull and Meninges.* By LEO M. DAVIDOFF, M.D., HAROLD G. JACOBSON, M.D., and HARRY M. ZIM-

MERMAN, M.D. 256 pages; 28 × 20 cm. Grune & Stratton, New York and London, 1961. Price, \$16.50.

Proceedings of the Conference on Physiological Aspects of Water Quality, September 8-9, 1960, Washington, D. C. Edited by HARRY A. FABER and LENA J. BRYSON. 244 pages; 26.5 × 20.5 cm. Published by Research and Training Grants Branch, Division of Water Supply and Pollution Control, U. S. Public Health Service, Washington 25, D. C.

Recent Advances in Human Nutrition. By J. F. BROCK, D.M. (Oxon.), F.R.C.P. (Lond.). 454 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1961. Price, \$11.50.

Textbook of Medicine. 13th Ed. Edited by Sir JOHN CONYBEARE, K.B.E., M.D., C.M. (Oxon.), F.R.C.P., and W. N. MANN, M.D. (Lond.).

F.R.C.P. 989 pages; 24 × 17 cm. E. & S. Livingstone, Ltd., Edinburgh and London, 1961. The Williams and Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$10.00.

Textbook of Pathology. An Introduction to Medicine. 7th Ed. By WILLIAM BOYD, M.D., M.R.C.P. 1,370 pages; 26 × 18.5 cm. Lea & Febiger, Philadelphia, 1961. Price, \$18.00.

Tumors of the Female Sex Organs. Part 3: Tumors of the Ovary and Fallopian Tube. (Atlas of Tumor Pathology, Section IX, Fascicle 33). By ARTHUR T. HERTIG, M.D. and HAZEL GORE, M.B., B.S. 176 pages; 26 × 20 cm. Published by the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington 25, D. C., 1961. Price, \$1.40 (paper bound).

MEDICAL NEWS

MEETINGS

- Aug. 27-Sept. 1. AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION, Sheraton-Cleveland Hotel, Cleveland. Dorothea C. Augustin, 30 N. Michigan Ave., Chicago 2, Executive Secretary.
- Sept. 27-29. AMERICAN ASSOCIATION OF MEDICAL CLINICS, Barbizon Plaza Hotel, New York. Dr. Joseph B. Davis, Clinic, 131 N. Washington St., Marion, Ind., Secretary-Treasurer.
- Oct. 1-7. COLLEGE OF AMERICAN PATHOLOGISTS, Olympic Hotel, Seattle. Dr. Arthur H. Dearing, Prudential Plaza, Suite 2115, Chicago, Executive Director.
- Oct. 18-20. MEETING OF AHA COUNCIL ON ARTERIOSCLEROSIS. The Council on Arteriosclerosis of the American Heart Association will hold its annual meeting at the Hotel Balmoral, Bal Harbour, Miami Beach, Florida, immediately preceding the AHA's annual scientific sessions in the same city, Oct. 20-22. All interested physicians, whether or not they are members of the Council, are invited to attend the sessions. Further information on the Council meeting may be obtained from Dr. Jeremiah Stamler, Chicago Board of Health, 54 West Hubbard St., Chicago 10, Ill., or from the American Heart Association, 44 E. 23rd St., New York 10, N. Y.
- Oct. 20-22. AMERICAN HEART ASSOCIATION—1961 SCIENTIFIC SESSIONS. Six sessions on clinical cardiology will be included in the 34th annual scientific sessions of the American Heart Association to be held at the Americana Hotel, Bal Harbour, Miami Beach, Florida. A panel or symposium including related investigative work will be presented at each clinical session. In addition, a total of 18 other scientific sessions will be held concurrently during the three day program. Registration forms, which include applications for hotel reservations, are available from the American Heart Association, 44 E. 23rd St., New York 10, N. Y.
- Oct. 22-25. AMERICAN COLLEGE OF GASTROENTEROLOGY, Hotel Cleveland, Cleveland. Mr. Daniel Weiss, 33 W. 60th St., New York 23, Executive Director.
- Nov. 5-8. ASSOCIATION OF MILITARY SURGEONS (68th annual convention), Mayflower Hotel, Washington, D. C. Rear Adm. Richard A. Kern, MC, USNR, Ret., 1726 Eye St., N. W., Washington 6, D. C., President.

- Nov. 9-11. GERONTOLOGICAL SOCIETY, INC., Penn-Sheraton Hotel, Pittsburgh, Pa. Gerontological Society, Inc., 660 South Kingshighway Blvd., St. Louis 10, Missouri.

INTERNATIONAL AND FOREIGN MEETINGS—1961

- Aug. 14-25. WORLD ASSEMBLY OF THE ISRAELI MEDICAL ASSOCIATION, Jerusalem, Israel. Dr. Leo Schindel, 20 Metudela St., Jerusalem, Israel.
- Aug. 28-Sept. 2. EUROPEAN SOCIETY OF HAEMATOLOGY, Vienna. Prof. Dr. H. Fleischhacker, Kongress-Sekretariat, Wien IX, Frankgasse 8, Billrothhaus, Austria.
- Sept. 4-7. TENTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES, Rome. Prof. C. B. Balabio, c/o Clinica Medica, Via F. Sforza 35, Milan, Italy.
- Sept. 15. INTERNATIONAL PANEL ON MULTIPLE SCLEROSIS, Rome. Giovanni Alemà, 7th International Neurological Congress, Viale dell Università 30, Rome, Italy, Secretary General.
- Oct. 15-20. FOURTH INTERNATIONAL CONGRESS OF ALLERGOLOGY, Hotel Commodore, New York City. Dr. William B. Sherman, 60 E. 58th St., New York 22, N. Y., Chairman.
- Nov. 27-29. AMERICAN SOCIETY OF HEMATOLOGY, Ambassador Hotel, Los Angeles, Calif. Dr. Louis Lowenstein, Royal Victoria Hospital, Montreal, Quebec, President.

POSTGRADUATE COURSES

UNIVERSITY OF CALIFORNIA AT LOS ANGELES

- Aug. 6-9. ADVANCED SEMINARS IN INTERNAL MEDICINE. Sun.-Wed. University Conference Center, Lake Arrowhead. \$137.50 (incl. room and meals). For information for physicians or ancillary personnel, contact Thomas H. Sternberg, M.D., Assistant Dean, Department of Continuing Education in Medicine and Health Sciences, UCLA Medical Center, Los Angeles 24.

UNIVERSITY OF SOUTHERN CALIFORNIA

- Aug. 2-18. HAWAII COURSE. The USC School of Medicine will offer the fourth postgraduate refresher course to be held in Honolulu and on board the S. S. Matsonia. (As a time and money saver, air travel is also possible.)
- Nov. 9-10. RECENT ADVANCES IN MEDICINE. Thurs.-Fri., Statler Hotel, Los Angeles. For

information contact Phil R. Manning, Assoc. Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 33.

FITZSIMONS GENERAL HOSPITAL, DENVER, COLO.

The fourteenth annual symposium on pulmonary disease will be held at Fitzsimons General Hospital, Denver, Colorado, September 25-29, 1961. This symposium is cosponsored by the American Trudeau Society, the University of Colorado School of Medicine, and Fitzsimons General Hospital. Tuition fee is \$5.00.

Information concerning enrollment may be obtained from the University of Colorado Medical School or from the Program Director, Colonel Charles S. Christianson, Pulmonary Disease Service, Fitzsimons General Hospital, Denver 30, Colorado.

ONE WEEK COURSE—ELECTRODIAGNOSIS AND ELECTROMYOGRAPHY

Sept. 18-22. The Department of Physical Medicine and Rehabilitation, New York Medical College—Metropolitan Medical Center announces a one-week course for physicians only in electrodiagnosis and electromyography. The course will consist of lectures, seminars, clinical demonstrations, and laboratory sessions. The teaching staff will include members of the faculty of the Medical College and noted guest lecturers. For applications and further information contact Raymond C. Lerner, M.S.S.W., Coordinator, Postgraduate Education, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 E. 105th St., New York 29, N. Y.

NEW YORK UNIVERSITY POSTGRADUATE MEDICAL SCHOOL, NEW YORK, N. Y.

Course No. 481 in occupational medicine will be given by the New York University Postgraduate Medical School, September 8-November 10, 1961. Tuition fee is \$375, field expenses \$25.

Further information can be obtained by writing the Office of the Associate Dean, New York University Postgraduate Medical School, 550 First Avenue, New York 16, N. Y.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Council on Postgraduate Medical Education of the American College of Chest Physicians will present the following postgraduate courses during 1961:

Sept. 25-29. INDUSTRIAL CHEST DISEASES. Warwick Hotel, Philadelphia.

Oct. 23-27. CLINICAL CARDIOPULMONARY PHYSIOLOGY. Sheraton-Chicago Hotel, Chicago.

Nov. 13-17. RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF HEART AND LUNG DISEASES. Park Sheraton Hotel, New York City.

Dec. 4-8. RECENT ADVANCES IN DISEASES OF THE CHEST. Statler-Hilton Hotel, Los Angeles.

Tuition for each course is \$75 for members of the American College of Chest Physicians and \$100 for non-members. The fee includes attendance at the round table luncheon discussions. For further information write Executive Director, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Ill.

INTERNATIONAL PSYCHOSOMATIC SEMINARS

During the winter of 1954-55, with the introduction of the World Medical Association and the American Psychiatric Association, Dr. J. L. McCartney was extended invitations to give lectures and clinics in twenty-five different ports visited by the American President Lines. A similar cruise is to be taken during the winter of 1962-63, and physicians interested in sharing their professional experience with practitioners around the world will be welcome to take part in the international psychosomatic seminars. The plan is to leave New York in October or November, 1962, and a teaching seminar will be held in every port visited. Ample time will be allowed for sightseeing. Reservations will have to be made well in advance, but if a sufficient number of qualified persons volunteer their services, then further psychosomatic seminars will be organized.

For further information write James L. McCartney, M.D., 223 Stewart Avenue, Garden City, N. Y.

EXAMINATIONS AND LICENSURE

AMERICAN BOARD OF PEDIATRICS: Written: Jan. 12, 1962. Oral: Atlantic City, April 28-May 1; San Francisco, June 15-18; Chicago, Oct. 6-8; and Pittsburgh, Nov. 30-Dec. 3. Final date for filing applications for the written examination is November 30, 1961. Dr. John McK. Mitchell, Rosemont, Pa., Secretary.

AMERICAN BOARD OF PREVENTIVE MEDICINE: Written examination in public health, aviation medicine, and occupational medicine, spring of 1962. Dr. Tom F. Wayne, 4219 Chester Ave., Phila. 4, Pa., Secretary.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Chicago, Oct. 9-10, 1961, and New

York, Dec. 11-12. David A. Boyd, Jr., 102-110 Second Ave., S. W., Rochester, Minn., Secretary.

MEDICAL PERIODICALS FOR THE WORLD MEDICAL ASSOCIATION

The World Medical Association is requesting that American physicians help to provide medical periodicals and books to foreign libraries, medical groups, and hospitals. It is requested that interested physicians provide the W. M. A. with the names of the periodicals which they are willing to send regularly overseas. Wrappers addressed to a foreign physician in need of a particular publication will be furnished the donor. For further information please write: World Medical Association, U. S. Committee, Inc., 10 Columbus Circle, New York 19, N. Y.

MEDICAL RESEARCH FELLOWSHIPS AND GRANTS

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1962, as follows: (1) *Until October 1, 1961*, for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipend \$4,500 with allowances for dependents and necessary travel; (2) *Until November 1, 1961*, for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 1030 East Lancaster Avenue, Rosemont, Pa.

FOURTH ANNUAL MMM AWARDS FOR MEDICAL WRITING

The Editors of *Modern Medical Monographs* announce the 1961 competition for unpublished manuscripts on clinical subjects in the field of internal medicine. The purpose of these annual awards, which are known as the *Modern Medical Monographs* Awards, is to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing.

The first prize is \$500. In addition, the authors of other top-ranking manuscripts which are found suitable will be offered a contract for publication of their work as a book in the series *Modern Medical Monographs* under standard royalty arrangements. The generosity and cooperation of Dr. Henry M. Stratton, President, Grune & Stratton, Inc., publishers of the series, have made these awards possible.

The entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association, and for clinical interest and scientific value by the editors and advisory board of *Modern Medical Monographs*.

Following are the rules of the competition:

1. The author must be a graduate physician, less than 40 years of age.
2. Manuscripts (including illustrations, if any) should be submitted in duplicate (original and one copy) by registered mail, postmarked no later than December 1, 1961, to Irving S. Wright, M.D., 450 East 69th Street, New York 21, N. Y.
3. The manuscript, including the bibliography, must consist of not less than 130, or more than 200, double-spaced typewritten pages with one-inch margins, and not more than 30 illustrations (pictorial charts, drawings, diagrams, or photographs).
4. Fishbein's book, *Medical Writing* (3rd Ed.), should be followed in preparation of the manuscript, use of abbreviations, etc., and bibliographic form.

INSTRUCTIONS TO AUTHORS

MANUSCRIPTS: All papers should be typewritten on one side of the paper and double spaced (including references, figure legends, and footnotes). The original and one carbon copy should be submitted with duplicate copies of all figures and tables. A separate title page should include the following: title, subtitle (if any), author(s) and his (their) degree(s), F.A.C.P. (if Fellow of the American College of Physicians), city or town where the work was done, hospital or academic institution (if any), and necessary acknowledgment of financial sponsors.

The introduction should orient the paper in relation to its field and should state its purpose. The main sections (for example, RESULTS) should be identified by centered headings in capital letters. Indicate further subdivisions by side headings that are flush with the left-hand margin and one line above the text, and/or by paragraph headings which should be indented on the first line of the paragraph and underlined. Extensive discussion should be separated from the presentation of the results. A succinct summary should state what was done, what was found, and what the findings are interpreted to mean. For guidance to sound grammar and clear style consult *The Elements of Style* by W. Strunk, Jr. and E. B. White, The Macmillan Co., New York, 1959.

ABBREVIATIONS, SYMBOLS, AND NOMENCLATURE: Abbreviations should conform as closely as possible to the *Style Manual for Biological Journals*, published in 1960 by the Conference of Biological Editors, Committee on Form and Style, American Institute of Biological Sciences, 2000 P Street, NW, Washington 6, D. C. Abbreviations should be kept to a minimum, should be defined when first used, and should be redefined in the summary; the forms of some frequently used abbreviations are listed at the bottom of this page. Generic names of drugs are preferred; a proprietary name may be given following the first use of the generic name. *Webster's New International Dictionary* is the standard reference for spelling, compounding, and hyphenating. Cardiopulmonary nomenclature is used as given in "Standardization of definitions and symbols in respiratory physiology," *Fed. Proc.* 9: 602, 1950.

REFERENCES: These are to be cited consecutively in the text as numbers enclosed in parentheses on the line of writing, not as superscript numbers. At the end of each article references should be listed in the numerical order in which they are first cited in the text. This list should conform to the style of the *Index Medicus* but with end pagination and number and month of issue omitted, and should be punctuated as in the following examples.

For journal articles: Surname and initials of author(s) (in capitals), title of article (lower case), name of journal (underlined for italics), volume number, first page, year. Thus:

4. DOE, J. E., ROE, R. C.: What I know about it. *Ann. Intern. Med.* 27: 1590, 1960.

For books: Surname and initials of author(s) (in capitals), title and subtitle (caps and lower case, underlined for italics), edition (other than first), publishing house, city, year, page or chapter as specific reference. Thus:

5. OSLER, W.: *Aequanimitas. With Other Addresses to Medical Students, Nurses and Practitioners of Medicine*, 3rd Ed., H. K. Lewis and Co., London, 1948, p. 250.

For articles in books: Surname and initials of author(s) (in caps), title of article (lower case), chapter number (if any), first page of article, title of book (caps and lower case, underlined for italics), editor, edition (other than first), publishing house, city, year. Thus:

6. WINTERNITZ, M. C.: Notes on an attack of coronary artery disease, in *When Doctors are Patients*, ed. by Pinner, M. and Miller, B. F., W. W. Norton and Co., New York, 1952, p. 31.

References to articles in press must state name of journal and, if possible, volume and year.

Authors are responsible for bibliographic accuracy; authors must check every reference in manuscript and again in galley-proof.

FOOTNOTES: Footnotes to tables should be designated by symbols in the following order: *, †, ‡, §, ||, #, **, ††, ‡‡, etc. Footnotes to the text should be as few as possible and should be typed at the foot of the appropriate page separated from the text by a ruled line.

TABLES: These should be typed on separate sheets with number and title (in caps) and centered. Symbols for units should be confined to the column headings. Vertical lines should be omitted. All data should be checked for accuracy.

FIGURES: These should be submitted in photographic form (glossy prints) or as original india ink drawings if no larger than standard page; poor free-hand lettering is not acceptable. Prints should not be mounted, stapled, or clipped. They should be labeled on back (lightly in pencil) with name(s) of author(s) and figure number, and the top indicated. Legends should be typed consecutively on a separate sheet. In photographs, identities of patients should be masked. In case of prior publication the author must obtain permission from the previous author and copyright holder to reproduce the figure in the ANNALS. Six illustrations are allowed without cost; above this number the actual cost is charged to the author.

ABSTRACTS: Each paper must be accompanied by an abstract typed in double space and in triplicate (for translation into Interlingua, for *Biological Abstracts*, and for the abstracting service of the J. A. M. A.). Title and authors should be given followed by a concise statement in not more than 250 words of (1) what was done, (2) what was found, and (3) what was concluded.

ABBREVIATIONS

intramuscular	im	centigrade	C	millimeter	mm	volume	vol
intraperitoneal	ip	Fahrenheit	F	centimeter	cm	milliliter	ml
intravenous	iv	specific gravity	sp gr	meter	m	liter	liter
subcutaneous	sc	hemoglobin	Hb	cubic millimeter	mm ³	concentration	concn
by mouth	po	pressure of CO ₂	P _{CO₂}	square meter	m ²	microequivalent	μEq
min. lethal dose	MLD	number	no.	weight	wt	milliequivalent	mEq
unit	U	standard deviation	sd	microgram	μg	millimolar	mM
international unit	IU	standard error	se	milligram	mg	milliosmole	mOsm
minute	min	probability	P	gram	g	milligram per cent	mg per cent
calorie (small)	cal	correlation coefficient	R	kilogram	kg		mg per 100 ml

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1. Jolliff, C. R., et al.: *Antibiot. Chemother. (Wash.)* 10:694, 1960.
2. Lippman, R. W., et al.: *J. Urol., Balt.* 80:77, 1958.

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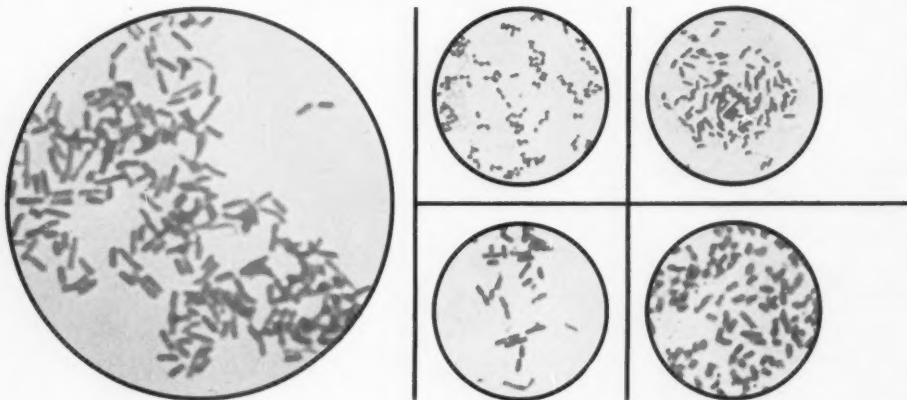


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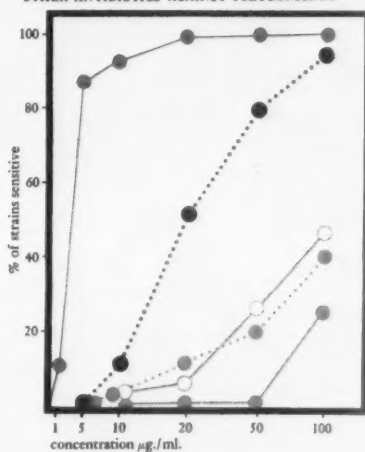
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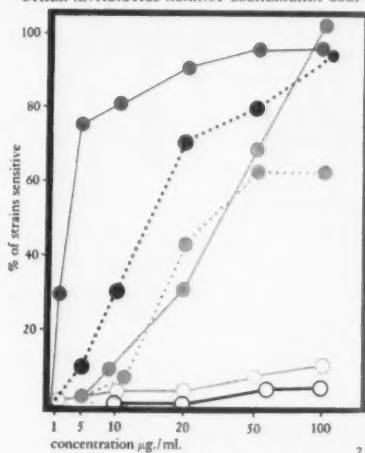
Supplied: In vials containing 150 mg. colistimethate sodium and 8 mg. dibucaine hydrochloride for reconstitution with 2 ml. sterile distilled water for injection. For intramuscular injection only.

References: 1. Carroll, G., and Malette, W. F.: J. Urol. 85:86, 1961. 2. Petersdorf, R. G., and Hook, E. W.: Bull. Johns Hopkins Hosp. 107:133, 1960. 3. Hall, J. W.: Am. J. M. Sc. 240:561, 1960. 4. Zinsser, H. H.; Lattimer, J. K., and Seneca, H.: J. Urol. 83:755, 1960. 5. Roberts, C. E., Jr., and Kirby, W. M. M.: Colistin in the treatment of hospitalized patients with *Pseudomonas* infections, presented at the 1960 Conference on Anti-Microbial Agents, Washington, D.C. 6. Schwartz, B. S., et al.: Antibiotics Annual 1959-1960, New York, Antibiotics, Inc., 1960, pp. 41-60. 7. Graber, C. D.; Tumbusch, W. T., and Vogel, E. H., Jr.: *Ibid.*, pp. 77-79. 8. Wright, W. W., and Welch, H.: *Ibid.*, pp. 61-74. 9. Ross, S.; Puig, J. R., and Zaremba, E. A.: *Ibid.*, pp. 89-100. 10. McCabe, W. R.; Jackson, G. G., and Kozij, V. M.: *Ibid.*, pp. 80-88. 11. Blaustein, A.: *Ibid.*, pp. 75-76. 12. Meleney, F. L., and Prout, G. R.: Surg. Gynec. & Obst. 112:211, 1961. 13. McCabe, W. R., and Jackson, G. G.: Am. J. M. Sc. 240:754, 1960. 14. Carroll, G.: J. Oklahoma M. A. 53:678, 1960. 15. Seneca, H.; Lattimer, J. K., and Zinsser, H.: New York J. Med. 60:3630, 1960.

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References: W. J. Kolff, "Acute Renal Failure: Causes and Treatment," *The Medical Clinics of North America*, 30:1052 (July 1955).
Peter Forsham, "Symposium on Adrenal Corticoid Therapy," *Metabolism*, 7:19 (Jan. 1958).

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references:

1. Graham, W.: *Canad. M.A.J.*: 82:1005 (May 14) 1960.
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Gastritis Symptoms Readily and Reliably Relieved

Complete relief of substernal or upper abdominal pain in 88 of 92 previously refractory patients with chronic gastritis¹ was obtained on *oxethazaine in alumina gel*, dietary controls, occasional gastric suction and rest. As therapy continued, dietary restrictions could be relaxed. No significant side effects developed even after 18 months' use.

In another study² of 56 patients with gastrointestinal disturbances—including 18 gastritis cases—53 patients displayed complete or partial relief when *oxethazaine in alumina gel* (or *alumina gel plus magnesium hydroxide*) was added to the therapeutic regimen.

Excellent Response Demonstrated in Other Gastrointestinal Disturbances

Oxethazaine in alumina gel is of value in a variety of other gastrointestinal conditions, including:

- peptic ulcer^{2,3} . . . relieves pain and promotes healing of duodenal and gastric ulcers
- esophagitis⁴ . . . relieves postprandial heartburn and acid regurgitation in chronic esophagitis without stricture
- irritable bowel⁵ . . . relieves discomfort and exaggerated gastrocolic reflex in the irritable bowel syndrome

- References:** 1. Deutsch, E., and Christian, H.J.: *J. Am. Med. Assoc.* 169:2012 (April 25) 1959.
2. Moffitt, R.E.: *Rhode Island Med. J.* 44:151 (March) 1961.
3. Hollander, E.: *Am. J. Gastroenterol.* 34:613 (Dec.) 1960.
4. Jankelson, I.R., and Jankelson, O.M.: *Am. J. Gastroenterol.* 32:636 (Nov.) 1959.
5. Jankelson, I.R., and Jankelson, O.M.: *Am. J. Gastroenterol.* 32:719 (Dec.) 1959.

For further information on limitations, administration and prescribing of OXAININE M and OXAININE, see descriptive literature or current Direction Circular.

NEW

a palatable suspension

OXAININE[®] M

Oxethazaine in Alumina Gel with Magnesium Hydroxide, Wyeth

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In 1961, you, the nation's physicians, will diagnose an estimated 70,000 cases of cancer of the colon and rectum.

Although potentially this is a highly curable cancer, each year more than two thirds of such patients die of the disease. Thousands are lost needlessly. They could be saved by proper medical treatment of the disease, found by annual examination, in its presymptomatic and most curable stage. The regular health checkup and alertness to first symptoms are great life-savers.

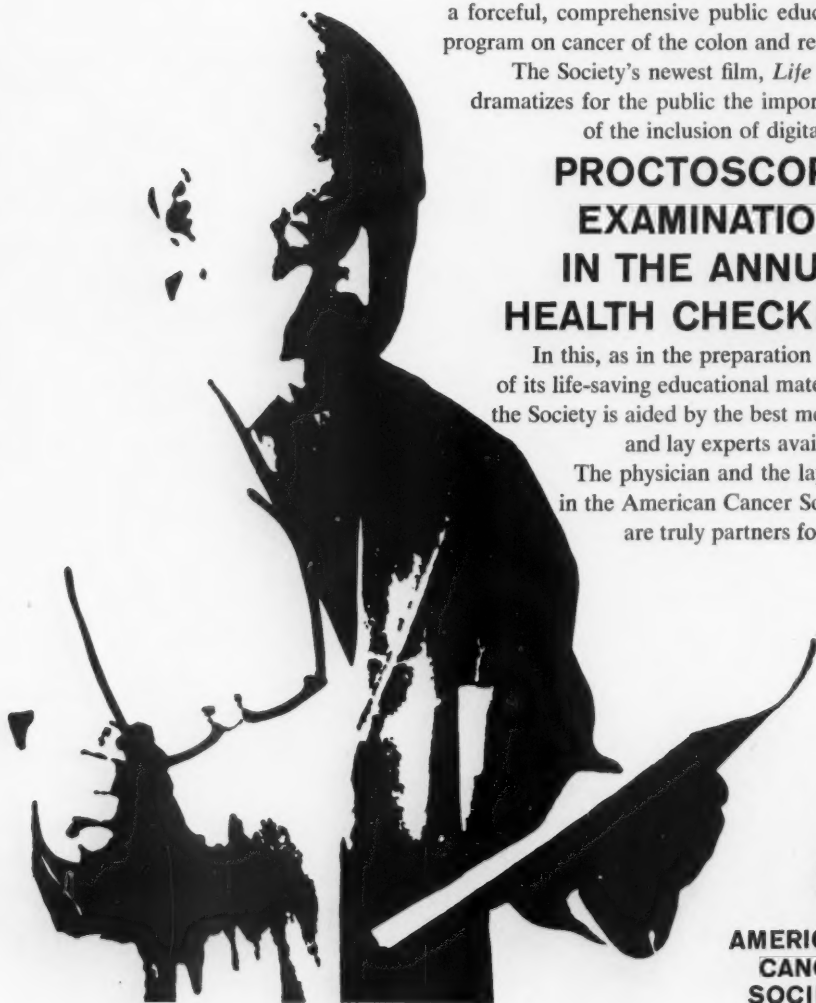
To help bring such patients to you *in time*, the American Cancer Society has developed a forceful, comprehensive public education program on cancer of the colon and rectum.

The Society's newest film, *Life Story* dramatizes for the public the importance of the inclusion of digital and

PROCTOSCOPIC EXAMINATIONS IN THE ANNUAL HEALTH CHECKUP.

In this, as in the preparation of all of its life-saving educational materials, the Society is aided by the best medical and lay experts available.

The physician and the layman in the American Cancer Society are truly partners for life.



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Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: 1. Ellis, L. B. *et al.*: *Circulation* 17:945, May 1958. 2. Friedlander, H. S.: *Am. J. Cardiol.* 1:395, Mar. 1958. 3. Riseman, J.E.F.: *New England J. Med.* 261:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.*: *Circulation* 12:169, Aug. 1955. 5. Russek, H. I.: *Am. J. Cardiol.* 3:547, April 1959. 6. Tortora, A. R.: *Delaware M. J.* 30:298, Oct. 1958. 7. Waldman, S. and Peiner, L.: *Am. Pract. & Digest Treat.* 8:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. before meals and at bedtime, according to individual requirements.

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Miltrate®

Miltown® (meprobamate) + PETN

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clinical experience continues to indicate
value of the CYTOTOXIC AGENT...

CYTOXAN[®]

Cyclophosphamide, Mead Johnson

for palliative chemotherapy of
certain types of malignant neoplasms

"Cyclophosphamide [Cytosan] has proved a valuable addition to chemotherapeutic drugs available for the treatment of malignant diseases of the haemopoietic and reticuloendothelial systems.... Particularly effective in Hodgkin's disease, lymphosarcoma, chronic lymphocytic leukaemia, and myelomatosis...."¹

"Objective data suggest that this agent [Cytosan] has advantages not possessed by standard alkylating agents now in clinical use."²

"With the use of cyclophosphamide [Cytosan] there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents."³

Other Advantages in Clinical Practice: Broad-spectrum application. High therapeutic index. No vesicant activity—may be given orally or parenterally.

(1) Matthias, J. Q.; Misiewicz, J. J., and Scott, R. B.: *Brit. M. J.* 2:1837-1840 (Dec. 24) 1960.

(2) Coggins, P. R.; Ravdin, R. G., and Eisman, S. H.: *Cancer* 13:1254-1260 (Nov.-Dec.) 1960.

(3) Papac, R.; Petrakis, N. L.; Amini, F., and Wood, D. A.: *J.A.M.A.* 172:1387-1391 (March 26) 1960.

DOSEAGE: For neoplasms relatively susceptible to Cytoxan

—Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2-3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intravenous dosage.

Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

For neoplasms relatively resistant to Cytoxan—Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourteenth day after the first dose of Cytoxan. Thrombocyte reduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu. mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

Leukopenia as a guide to adequacy of dosage—The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient. Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leukopenic patients must be watched carefully for evidence of infection.

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate therapy and to adjust dosage.

SIDE EFFECTS: Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the

tumor, when indicated. It is apparently active by each of these routes.

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with other chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.

ADMINISTRATION: Add 5 cc. sterile water (Water for Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing if the solution is glucose or saline.

No thrombosis or thrombophlebitis has been reported from injections of Cytoxan. Extravasation of the drug into the subcutaneous tissues does not result in local reactions.

PRECAUTIONS: Cytoxan should not be given to any person with a severe leukopenia, thrombocytopenia, or bone marrow infiltrated with malignant cells. It may be given with suitable precautions to patients who have had recent x-ray treatment, recent treatment with a cytotoxic agent, a surgical procedure within 2-3 weeks, or debilitated patients.

AVAILABILITY: Cytoxan is available as follows:

Cytosan for Injection, 100 mg., a sterile dry-filled vial containing 100 mg. cyclophosphamide and 45 mg. sodium chloride. Packaged, 12 vials per carton.

Cytosan for Injection, 200 mg., a sterile dry-filled vial containing 200 mg. cyclophosphamide and 90 mg. sodium chloride. Packaged, 12 vials per carton.

Cytosan Tablets for oral administration, 50 mg., white, round tablets, flecked with blue for easy identification. Packaged, 100 tablets per bottle.

For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department, Mead Johnson Laboratories, Evansville 21, Indiana.



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In hypoprothrombinemia

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Rapid action

rate of absorption faster than menadione or derivatives...more potent and lasting effects.

Wide margin of safety

substantially safer than vitamin-K analogues—no kernicterus reported.

Versatility of administration

capsules for oral use...fine aqueous dispersion for parenteral administration.

Compatibility

unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.

Low dosage forms

no excess, no waste—packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

Capsules—5 mg; Ampuls—1 mg/0.5 cc

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1. The whole root, including all its active fractions, is used for maximal antihypertensive activity with minimal sedation.



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to relieve tensions and to inhibit
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highly effective with minimal side effects for therapeutic/prophylactic treatment of duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, gastric hypermotility. PATHIBAMATE-400 (full meprobamate effect)—1 tablet t.i.d. at mealtime, and 2 tablets at bedtime • PATHIBAMATE-200 (limited



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**in severe drug and food sensitivity...
rapid relief and control
of symptoms on short-term
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Brief treatment with DECADRON — orally or parenterally — can provide rapid and effective control of allergic emergencies and acute allergic disorders such as reactions to foods, drugs, plants, weeds, and animals. In 40 patients given Injection DECADRON Phosphate, "subjective improvement was often noticed within one hour and objective improvement recorded within 4 hours."¹ Therapeutic doses of steroids may help prevent recurrences of severe allergic states, without interfering with desensitization or other immunity procedures.²

Before prescribing or administering DECADRON, the physician should consult the detailed information on use accompanying the package or available on request.

References: 1. Grater, W.C.: Southern M. J. 53:1144, 1960. 2. Feinberg, S. M.: Med. Sci. B. (No. 3) 181, 1959.

Supplied: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100 and 1000. As Injection DECADRON Phosphate in 5 cc. vials, each cc. containing 4 mg. of dexamethasone 21-phosphate as the disodium salt; inactive ingredients: 8 mg. creatinine, 10 mg. sodium citrate; sodium hydroxide to pH 7.8, and water for injection q. s. 1 cc.; preservatives: 0.32 per cent sodium bisulfite and 0.5 per cent phenol. DECADRON is a trademark of Merck & Co., Inc.

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Dexamethasone
TREATS MORE PATIENTS MORE EFFECTIVELY

DECADRON: Recommended dosage schedule in the treatment of drug and food sensitivity reactions

time	amount	administration
1st day	one to two cc. (4 to 8 mg.) Injection DECADRON Phosphate intramuscular	repeated as necessary (In substituting tablet therapy, give the first oral dose four or five hours before the final parenteral dose.)
2nd day	two 0.75 mg. Tablets DECADRON	b.i.d.
3rd day	two 0.75 mg. Tablets DECADRON	b.i.d.
4th day	one 0.75 mg. Tablet DECADRON	b.i.d.
5th day	one 0.75 mg. Tablet DECADRON	per day
6th day	one 0.75 mg. Tablet DECADRON	per day
7th day	RETURN VISIT	



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ON SIMPLE DOSAGE SCHEDULE

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DURA-TAB S.M.[®]

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Stewart¹ found the "significantly prolonged therapeutic serum quinidine levels" with QUINAGLUTE DURA-TAB S.M. provide...

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- Better toleration because quinidine gluconate is more soluble and less irritating to the G.I. tract than the sulfate.
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QUINAGLUTE DURA-TAB S.M. ... a quinidine of choice in atrial fibrillation, auricular tachycardia, flutter.

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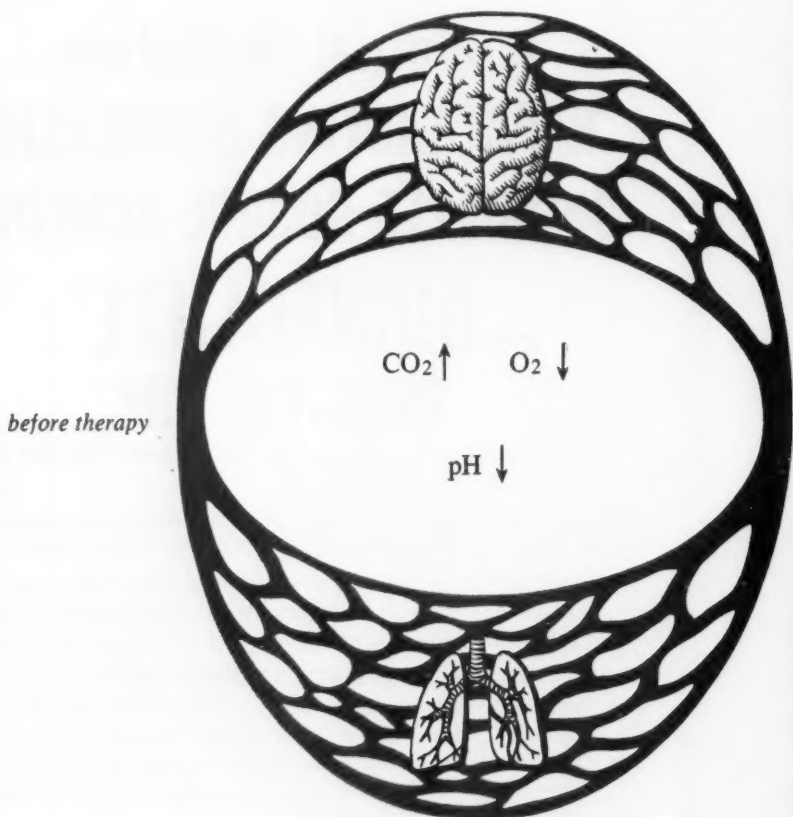
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in respiratory disease

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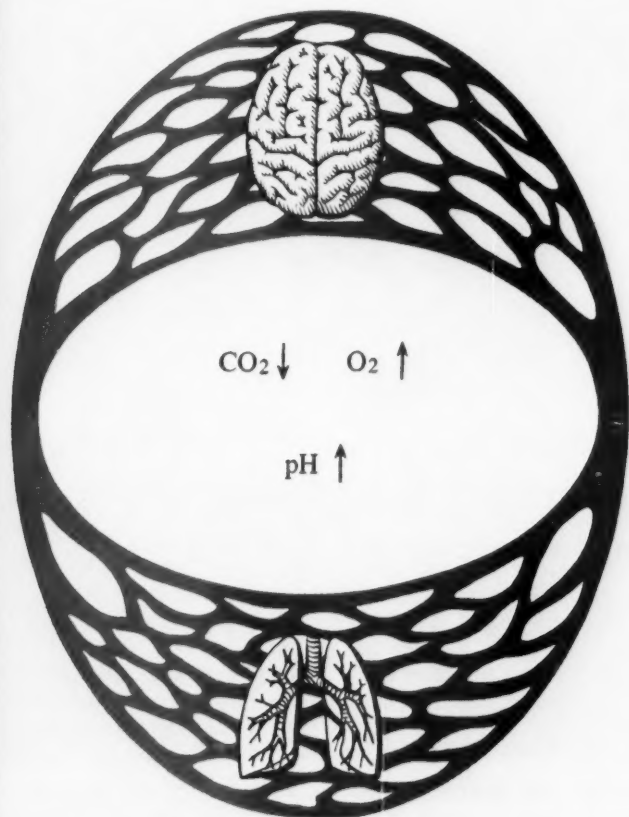
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Consider that their specific complaints may be the consequences of CO₂ retention (*hypercapnia*) and secondary reduced oxygen saturation (*hypoxia*) due to hypoventilation.

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EMIVAN selectively stimulates the medullary respiratory center to increase the *depth* of breathing and (to a lesser extent) the *rate* of breathing . . . *without* cardiovascular side effects, neurological damage, or secondary post-stimulatory depression.



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INTRAVENOUS EMIVAN, can be life-saving



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YES . . . The evidence is impressive that Vaponefrin Solution (racemic epinephrine) delivered with the patented Vaponefrin Nebulizer, is not only effective but also eminently well tolerated and relatively safe for the treatment of emphysematous patients with cardiovascular complications.

"The effect is seen at the site where the process that we wish to treat exists, and systemic toxicity usually is negligible. Even in patients with severe hypertension the administration of epinephrine [Vaponefrin] by this route is not harmful..."¹

"The authors have used the racemic epinephrine [Vaponefrin] most commonly and have not observed any untoward changes in hypertensive or cardiac patients."²

"...the simultaneous presence of hypertension, rheumatic heart disease, cardiac disturbance due to arterial disease, or diabetes, is not a contraindication..."³ to Vaponefrin.

Over 160 clinical references* published in leading journals and textbooks demonstrate that along with an outstanding record of safety, Vaponefrin quickly improves vital capacity-time relationships,⁴ markedly increases maximum breathing capacity, increases expiratory velocity, and minimizes air "trapping".⁵

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*Bibliography and demonstration set available upon request.

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"The therapeutic index as defined in this study reflects clinical usefulness and indicates to what degree a sedative agent approaches the ideal."¹ It is significant that phenobarbital, although widely used in anxiety states, falls far short of the ideal.¹

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1. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, *Postgrad. Med.* 26:502-509 (October) 1959.



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**just one tablet of Midicel
provides continuous, effective
blood levels for 24 hours**

Because many patients need take only 1 tablet daily, therapy with MIDICEL is convenient and economical. It is also advantageous since the possibility of omitted doses is reduced. Rapidly absorbed and slowly excreted, MIDICEL assures dependable bacteriostatic action in urinary tract infections, certain respiratory infections, bacillary dysenteries, as well as surgical and soft-tissue infections caused by sulfonamide-sensitive organisms. And with MIDICEL, there is little likelihood of crystalluria because of its high solubility and low dosage.

MIDICEL (sulfamethoxypyridazine, Parke-Davis), 3-sulfanilamido-6-methoxypyridazine. Tablets of 0.5 Gm.; Suspension, each cc. containing 50 mg. of sulfamethoxypyridazine as the N'-acetyl derivative. *Indications:* Gram-negative and gram-positive infections such as urinary tract, respiratory, and soft-tissue infections and bacillary dysenteries. *Dosage:* Orally once a day until asymptomatic for 48 to 72 hours. Adults:—1 Gm. initially, followed by 0.5 Gm. daily thereafter or 1 Gm. every other day. In severe infections, not to exceed 2 Gm. the first day, then 0.5 to 1.5 Gm. daily according to weight of patient and severity of

infection. Children:—30 mg. per Kg. the first day, then 15 mg. per Kg. daily. In severe infections, up to 50 mg. per Kg. initially, then 25 mg. per Kg. daily. Total dose in children, however, should not exceed lower dosage limits for adults. *Precautions:* Continue daily doses higher than 0.5 Gm. no longer than three to five days without checking for blood levels above therapeutic range. Maintain adequate fluid intake during therapy and for 48 to 72 hours afterward. Until further definitive information is available, MIDICEL, in common with all sulfonamides, is contraindicated in the premature and newborn infant. Contraindicated in patients with a history of sulfa sensitivity. MIDICEL is not recommended for meningococcal infections. *Side Effects:* Anorexia and lassitude may occur as may reactions such as drug fever, rash, and headache, all of which are indications for discontinuing the drug. Leukopenia has been reported. Periodic blood counts are advised. Patients with impaired renal function should be followed closely since excessive accumulation may occur. **AVAILABLE:** Quarter-scored tablets of 0.5 Gm., bottles of 24, 100, and 1,000.

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and for children... Midicel Acetyl Suspension (N' acetyl sulfamethoxypyridazine, Parke-Davis) • delicious butterscotch flavor • only one dose a day

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A 5-year study¹ of long-term anticoagulation with COUMADIN (warfarin sodium) in office practice patients has demonstrated that such treatment reduces the probability of further infarctions in the postinfarct patient and is effective in preventing a first infarction in patients with angina.

An earlier report² noted that long-term anticoagulant therapy with warfarin sodium can be carried out, along with the necessary prothrombin time determinations, as part of general office practice.

"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of Warfarin sodium [COUMADIN]."¹

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Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

1. Nora, J. J.: *M. Times*, May, 1961. 2. Nora, J. J.: *J.A.M.A.* 179:118, Sept. 10, 1960. 3. Baer, S., et al.: *J.A.M.A.* 167:704, June 7, 1968. 4. Moser, K. M.: *Dis-ease-a-Month*, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13. 5. Meyer, O. O.: *Postgrad. Med.* 24:110, Aug., 1958.

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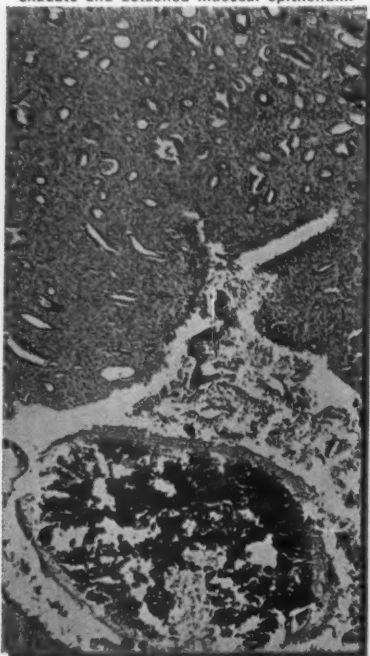
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GOUT

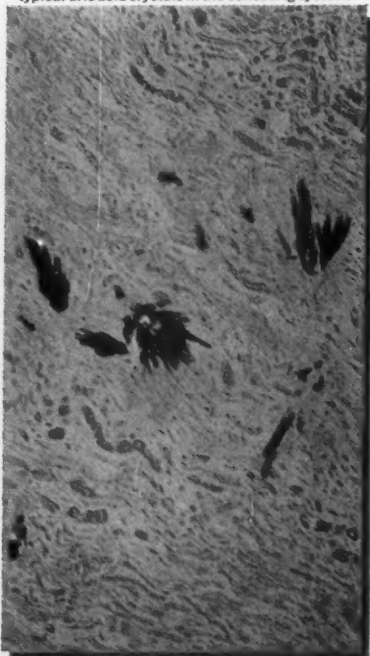
"For centuries the victims of gout have been the subject of lampoons and caricatures. We now know that they should rather be the objects of great concern, for the disease is painful, disabling and is accompanied by complications that impair health and shorten life."¹

Kidney impairment, with varying degrees of hypertension and arteriosclerosis, is the critical complication of gout. "From 30 to 50 per cent of gouty patients are said to die of renal disease."²

Tophus in the calyx, surrounded by fibrinoid exudate and detached mucosal epithelium.³



The mid- and outer portion of the pyramid with typical uric acid crystals in the collecting system.³

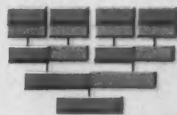


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Gout... acutely painful attacks followed by periods of remission.



"If a family history of gout is obtained, even though it is one or two generations removed, this information is significant."⁴



"The metatarsophalangeal joint of a great toe is affected early or repeatedly in some cases, rarely or never in others."⁵



"All patients complaining of non-traumatic musculoskeletal discomfort should have at least one serum uric acid determination."⁵



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"Of the various drugs with uricosuric activity, probenecid [BENEMID] has proved most desirable for long-term administration."⁸

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1. Cornish, A. L.: *Kentucky M.A.* 58:707, June, 1960. 2. Wyngaarden, J. B.: *Arthritis & Rheumatism* 1:191, June, 1958. 3. Talbott, J. H. and Terplan, K. L.: *Medicine* 39:405, Dec., 1960. 4. Talbott, J. H.: *Gout*, New York, Grune & Stratton, 1957, p. 123. 5. Kuzell, W. C., et al.: *J. Chron. Dis.* 2:645, Nov., 1955. 6. Hench, P. S.: *Gout and gouty arthritis*, in Cecil, R. L.: *A textbook of medicine*, ed. 10, Phila., W. B. Saunders Co., 1959. 7. Bartels, E. C., and Kopley, P. H.: *Bull. Vancouver M.A.* 28:306, April, 1953. 8. Boland, E. W.: *World-Wide Abstracts of Gen. Med.* 9:16, Jan., 1960. 9. Talbott, J. H.: *Current Med. Dig.* 26:57, Nov., 1959.

Before prescribing or administering BENEMID or ColBENEMID, the physician should consult the detailed information on use accompanying the package or available on request.



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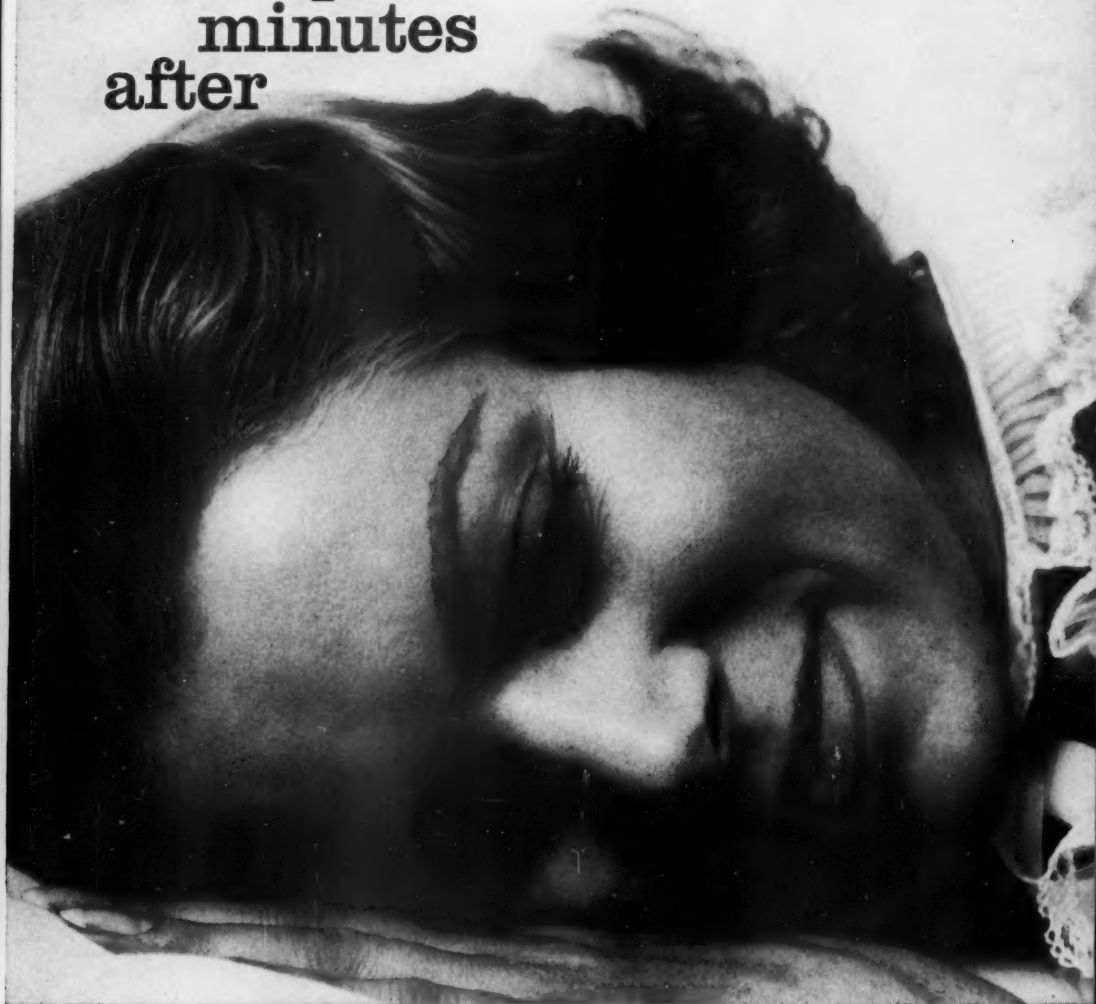
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1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.
2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.



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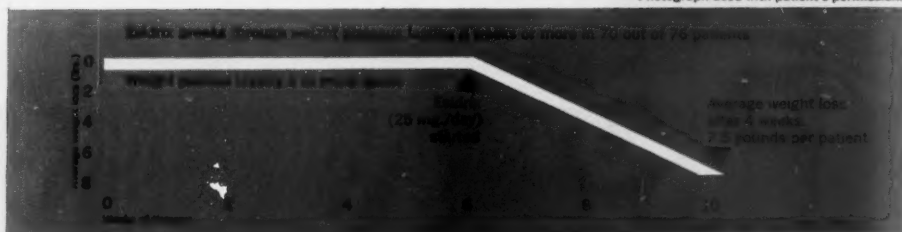
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References: 1. Ray, R. E.: To be published. 2. Einhorn, H. P., and Kalb, S. W.: Clin. Med. 7:1995 (Oct.) 1960.

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References: 1. David, N. A.; Porter, G. A.; and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Fuchs, M.; Moyer, J. H.; and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 3. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

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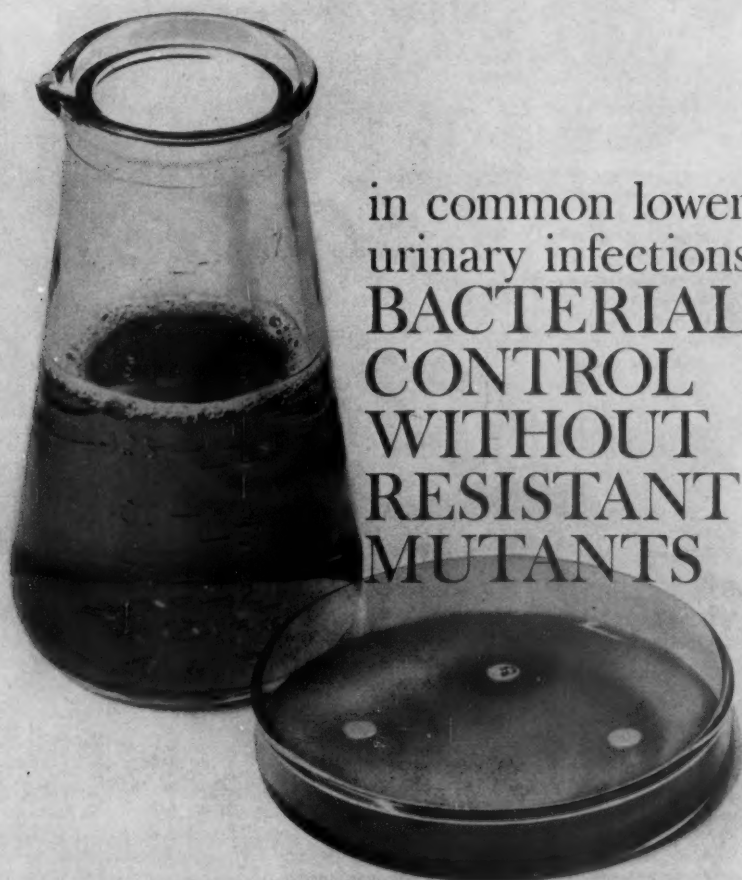
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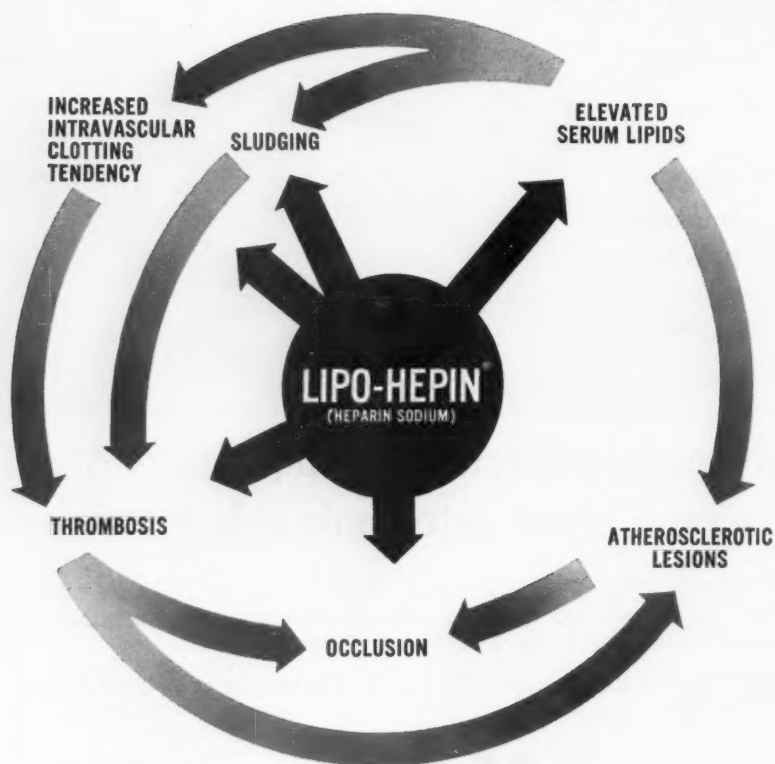
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1. Shlevin, E. L.: Pregnancy and Diabetes, Diabetes, 6:523, 1957.

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Volume 55

JULY 1961

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